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PATHOLOGICAL LABORATORY

Aldred Scott Warthin, Ph.D., M.D., Director

REPRINTS
VOLUME VI
1913—1914

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ANN ARBOR, MICHIGAN
1914

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Heredity with Reference to Carcinoma

As Shown by the Study of the Cases Examined in the Pathological Laboratory of the University of Michigan, 1895-1913

ALDRED SCOTT WARTHIN, M.D.
ANN ARBOR, MICH.

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*Reprinted from the Archives of Internal Medicine
November, 1913, Vol. 12, pp. 546-555*

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CHICAGO
American Medical Association
Five Hundred and Thirty-Five North Dearborn Street
1913

HEREDITY WITH REFERENCE TO CARCINOMA

AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN,

1895-1913

ALDRED SCOTT WARTHIN, M.D.
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The statistical study of carcinoma is regarded by many writers as having been carried as far as it can be profitable; and certainly but little that is new has been gained through this method during the last decade. Nevertheless, its possibilities have not been exhausted; and it is highly desirable that the whole neoplasm problem in all of its aspects be attacked again from the statistical standpoint, though in a somewhat different way. Practically all of the old statistical studies of neoplasms, particularly those of carcinoma, were based on mortality reports; or if not on these, on morbidity reports based on clinical diagnoses. In very few instances only has the statistical study been carried out on the basis of the records of a diagnostic pathological laboratory. Statistics of neoplasm from such a source must be of infinitely greater value than those founded on mortality statistics. In the records of the diagnostic laboratory the diagnosis is based on the histological examination, and the percentage of error is reduced to a minimum. In the mortality statistics, on the other hand, the diagnoses are chiefly clinical, and consequently subject to the wide error inherent in the clinical diagnosis of "tumor," neoplasm, "cancer" and the like. Moreover, the material coming to the diagnostic laboratory is usually seen from two to five years earlier than the mortality age. In studies relating to the age-incidence of any form of neoplasm it is evident that the records of the pathological laboratory for that neoplasm will be much more trustworthy than the mortality statistics. It is also possible many times in the diagnostic laboratory to follow the course of a neoplasm over a definite period, so that important practical knowledge may be gained as to rate of growth, recurrence, healing, metastases, etc.

The following study of the influence of heredity on carcinoma is taken from the records of the pathological laboratory of the University of Michigan during the years of my service from 1895 to 1913. During this period 3,600 cases of neoplasm of all varieties have been studied, either in material taken for practical diagnosis or obtained by necropsy. Of these 3,600 cases, some 1,600 were cases of carcinoma, as was shown by the microscopic diagnosis. Practically every variety of carcinoma described in the literature, and a few others, as well, are to be found in this material; and the same is true of the other forms of neoplasm. While carcinomas of the breast, uterus and lip form the greater part of the cases examined, all other localizations are represented. Another great advantage is that about 90 per cent. of the material was derived from the general population of the state of Michigan. The fact that the university hospital is a state hospital and not a charity institution, gives it a much more representative population than would be found in the charity hospitals of the greater cities.

The difficulty of obtaining a family history from patients in charity hospitals is well known. Few of them know the cause of death in their grandparents or in other members of that generation. The same thing is true, though to a less extent, of the patients from whom the material used in this study was obtained. Therefore what worth this study may have must be positive; the negative findings cannot be taken as absolute. In about six hundred cases of carcinoma no family history was obtainable; in the majority of those in which a family history was obtainable the details are meager. In spite of these handicaps, in a surprisingly large number of cases a family history of carcinoma is given — about 15 per cent. of all in which the family history is obtainable.

The existence of a family susceptibility to carcinoma, denied by many writers, affirmed by others, has again become, as a result of the studies of endemic carcinoma in mice, a question exciting lively interest. These investigations appear to show that certain family strains in mice do not develop spontaneous tumors, and that, further, such strains are resistant to tumor transplantation from other mice. Other family strains show a high frequency of spontaneous tumors, and in such strains transplantation may be successfully carried out. It would appear then, that the latter strains possess a familial predisposition or susceptibility to the development of neoplasm, and that intrinsic or inherited factors play some part in the development of neoplasms. Bashford denies this, and Tyzzer, who carried out breeding experiments with animals representing different strains, was unable to find that the transmission of the predisposition to neoplasm followed the laws of heredity.

On the other hand, a family predisposition in the human species to certain forms of neoplasm has long been recognized, particularly in the case of certain benign neoplasms (fibroma, lipoma, chondroma, osteoma, angioma, leiomyofibroma, glioma, neurofibroma, papilloma, adenoma and cyst-adenoma), and to a less marked degree in the case of certain forms of sarcoma and carcinoma. While the existence of such a predisposition is generally accepted by text-books on pathology, no good statistical studies exist of the hereditary occurrence of these neoplasms.

Cancer surveys of living patients, as conducted in Germany some years ago, have given little information concerning the family occurrence of neoplasms, chiefly for the reason that it is practically impossible to trace the members of a given family through more than one or two generations, and unless all of the members of the family for several generations can be considered, no accurate conclusions can be drawn. The difficulties attendant on such a statistical study are very great; and except in rare cases complete family records of cancer incidence are not found in the literature. One of the most striking is Broca's case,[1] also quoted by Levin, who criticizes the method of investigation, because no comparison was made between the number of the affected and unaffected members in each generation. If the total number of ascendants is not considered, and only those affected by carcinoma picked out, a family may appear to be a cancer family when in reality the proportion of cancerous to non-cancerous members is very small. As Levin states, Broca's family might give very different results if studied from the standpoint of the history of all its members.

Levin, to my knowledge, is the only one who has attempted a statistical study of heredity in cancer from the standpoint of an entire family history. He collected data[2] from five families, in two families fairly complete and in three fragmentary. In the families studied he noted that they were characterized on the whole by the occurrence of cancer of the intestines in the males, and cancer of the breast in the females. His charts show that the incidence of cancer in these families is not greater numerically than would be found in the population as a whole, but that the occurrence of "cancerous fraternities" (a fraternity in which one or more members suffer from cancer, with a history of cancer either on the maternal or paternal side, or both) speaks for some influence of heredity on cancer. In other words, a cancerous fraternity must mean the union of two germ-plasms, each of which is characterized by the presence of germ-cells that are non-resistant to cancer.

In my material of 3,600 cases of neoplasm examined pathologically, there were 1,600 cases of carcinoma. About one thousand of these gave fairly good family histories with the ages of the members. A smaller number (30 per cent.) gave detailed histories. From this number are taken the families which show multiple occurrence of carcinoma. In many of these all of the members of the family for three generations are given; in others, the records are incomplete. Four families give complete records of the descendants of the cancerous grandparent. The incidence of cancer in these families is so striking that it can be interpreted as showing an inherited susceptibility to cancer.

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[1] Broca: Quoted by Wolf, Die Lehre von den Krebskrankheiten, Jena, 1907; Williams, p. 369.

[2] Levin: Ztschr. f. Krebsforsch., 1912, ix, S. A., p. 5.

Family G. (Chart 1).—In this family a fairly complete survey was made of the two generations derived from a cancerous grandfather with a traditionary history of cancer in his line and a grandmother with a normal family history. From these there were ten children, five males and five females. Two of the daughters died of cancer of the uterus at 55 and 40 years, while two sons died at 42 of cancer of the stomach, and a third one at 45 of cancer of the abdomen. All five of these individuals were married to normal partners without a family history of cancer, and all had issue, as follows: Oldest daughter who died at 55 of cancer of the uterus, had ten children: one daughter operated on at 42 for "cancer" of the uterus and still living; another daughter operated on at 22 for uterine tumor and bilateral dermoids of ovary, and still living. The remaining eight children are all living and well, only two being over 40 years of age. The second daughter, who died at 40 of cancer of the uterus, had four children, two sons and two daughters all dying of cancer, the two sons of cancer of the stomach and intestine, and the two daughters of carcinoma of the uterus. The third daughter, living and well at the age of 75, has three normal children living at the ages of 47, 50 and 55. Four children had no living issue. The eighth child, a son, died at 42 of cancer of the stomach. His wife was of normal family history. They had eight children, of whom two daughters have died of cancer of the uterus at 40 and 44 years, while the remaining six are all living and well below the age of 40. The ninth child, a son, died of cancer of the stomach when between 40 and 42 years of age. He left six children from a marriage contracted with a woman of non-cancerous family history. One daughter died at 42 of cancer of the uterus, three children died of tuberculosis between the ages of 18 and 25 years, while two others are living and well at the ages of 32 and 29 years. The tenth son died at 45 of cancer of the abdomen, most probably primary in the stomach. He left, from a marriage contracted with a woman of non-cancerous family, seven children, of whom one died at 42 of cancer of the stomach and liver, another at 47 of cancer of the intestine, while a third was operated on at 42 for tumor ("cancer") of the uterus, and still lives in apparent good health. Four others are living and normal at the ages of 45, 35, 30 and 30.

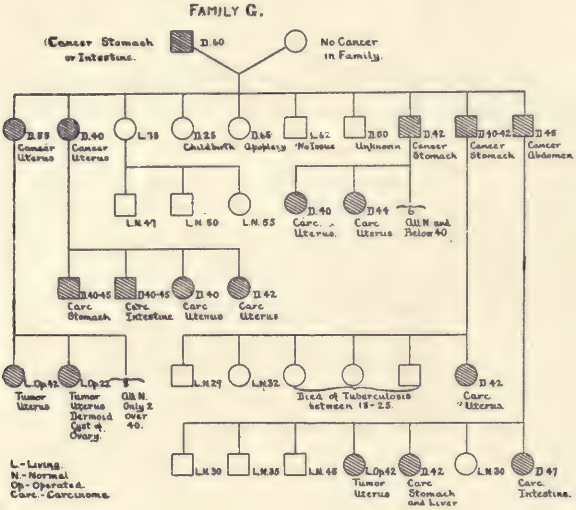

Chart 1

Of the forty-eight descendants of the cancerous grandfather seventeen have died or been operated on for "cancer." The preponderance of carcinoma of the uterus (ten cases) and of the stomach (seven cases) is very striking in the family history.

Family F. (Chart 2).—In this family the maternal grandmother died of tumor. Her non-cancerous brother had two children, both of whom died of "cancer." Her only son died at 61 of dropsy. He married a woman who had two brothers who died of cancer of the stomach. She herself died of Bright's disease at 75. Her mother died of heart disease. The three daughters of this pair who show a double family history of susceptibility to cancer all had neoplasms; the oldest was operated on for tumor ("cancer") of the uterus and is still living; the second was operated on at 51 for myosarcoma of uterus, while the third daughter died of cystic tumor of the ovary. In this family history the preponderance of stomach and uterine neoplasms is also shown.

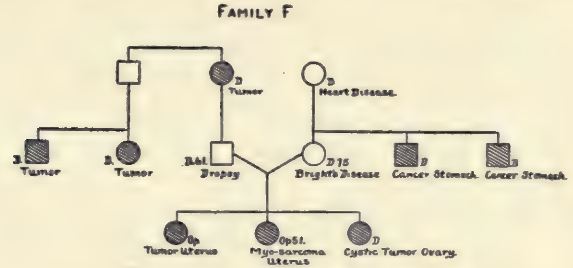

Chart 2

Family P. (Chart 3).—The paternal grandfather had a nephew who died of cancer of the lip. In the first filial generation there was one daughter who died at 35 of cancer of the lip and a son who died at 86 of cancer of the scalp and cervical lymph-nodes. This son married a non-cancerous woman whose only sister had died at 47 of cancer of the rectum. From this union thirteen children, ten of whom (five brothers and five sisters) all died of pulmonary tuberculosis before the age of 30, while three remaining daughters had carcinoma of the breast, two dying at the ages of 36 and 42, and one operated on at 35.

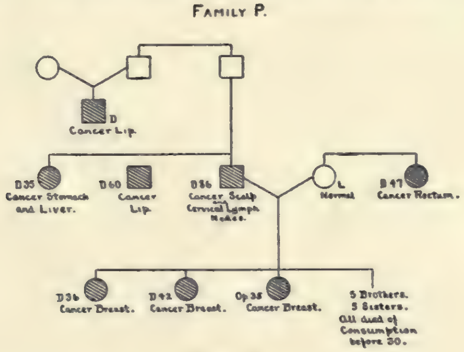

Chart 3

Family S. (Chart 4).—The paternal great-grandfather died at about 70 of cancer of the stomach. His only son died at about 60 of cancer of the stomach, having married a woman who died at about 50 of cancer of the breast. They had six children, all of whom died of cancer; two daughters died at 80 and 60 of cancer of the breast, and another at 60 of multiple carcinoma of the breast, bladder and rectum. Two sons died of cancer of the stomach at the ages of 75 and 40, the third son dying of cancer of some internal organ, most probably the stomach. Only one son had issue, by marriage with a normal line. The only child died at 36 of cancer of the uterus. Of the eight descendants of the cancerous great-grandfather all died of cancer. As in Family P., the occurrence of carcinoma in both paternal and maternal lines apparently strengthens the susceptibility, both families becoming extinct.

CANCEROUS FRATERNITIES

These are of much more frequent occurrence in the case-histories of carcinoma (Charts 5, 6, 7, 8, 9) than the striking family histories given above show. The reasons for this are obvious: Few individuals of the

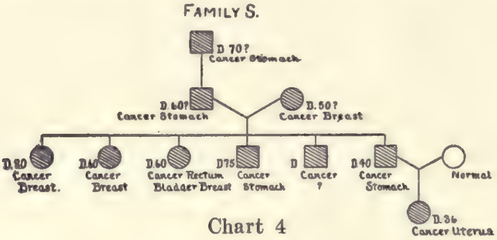

Chart 4

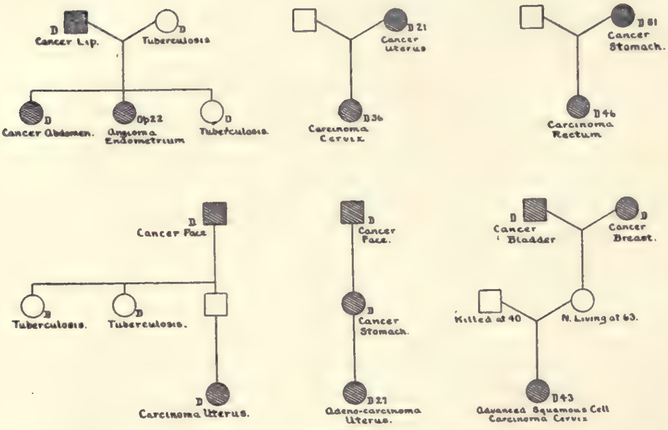

Chart 5

general run of the American population know anything about their family history except for the immediate members. By far the majority do not know the cause of death of their grandparents. Twenty-nine cancerous fraternities are selected as representative of our case-histories. Two generations only are represented in the majority, but in some of them three generations, and in one instance, four generations are shown. The normal members of the second and third generations are also given, so that the proportion of cancerous to non-cancerous individuals in two generations is exact. The majority of the cancerous fraternities occur in small families, and in many cases the patient from whom the material examined came represented the end of the family line. In several instances all the members of the small family are cancerous. The charts explain themselves. The most striking thing shown, aside from the susceptibility of the family group, is the great prominence of tuberculosis as the most commonly associated disease of the cancer stock. The two susceptibilities seem to run together, at least, in so far as our family histories are concerned. A tuberculous ancestry is not infrequently found in families where there is no family history of cancer back of the present

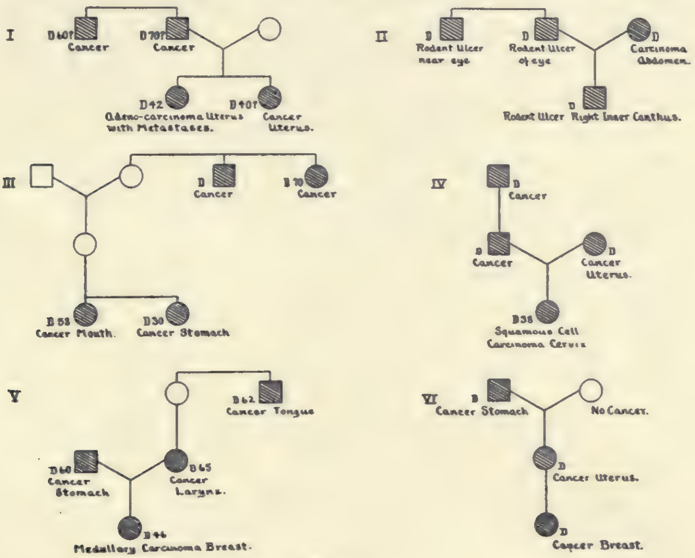

Chart 6

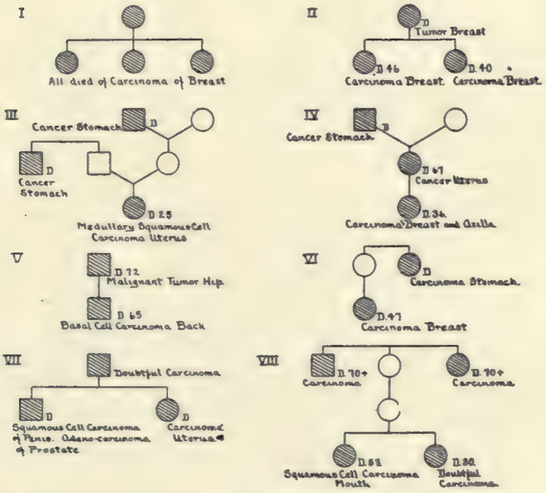

Chart 7

generation. Next to tuberculosis the diseases most commonly associated with carcinoma are cardiac and renal disease.

It will be noted that the uterus, breast, gastro-intestinal tract and mouth are the parts of the body most frequently involved in the case of these family cancers. Cancer of the lip and rodent ulcer of the face show also a tendency to family occurrence.

The study of a large number of cases of carcinoma yields isolated but striking examples of a marked family occurrence through several generations; and a much more frequent family group or "cancerous fraternity" occurrence. From such histories it is hardly possible to draw any other conclusion than that a definite cancer susceptibility exists in certain families. The great frequency of the association of cancer with tuberculosis might be taken as an evidence of a general weakened resistance on the part of the family lines; and this conclusion is supported by the extinction of many of these lines through a lessened fertility.

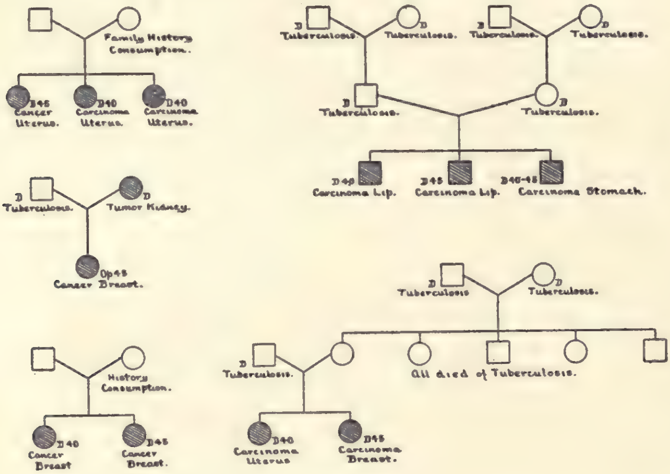

Chart 8

In the study of all of our neoplasm material a family susceptibility is occasionally shown in the case of angioma, lymphangioma, fibroma, neurofibroma, lipoma, myofibroma of uterus, adenoma of breast and adenoma of thyroid; but extremely rarely in the case of sarcoma.

CONCLUSIONS

1. A marked susceptibility to carcinoma exists in the case of certain family generations and family groups.

2. This susceptibility is frequently associated with a marked susceptibility to tuberculosis, and also with reduced fertility.[3]

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[3] The striking association of tuberculosis with cancer in certain families has also been noted by Kuthy and Williams, "The Natural History of Cancer," p. 371.

3. The multiple occurrence of carcinoma in a family generation practically always means its occurrence in a preceding generation.

4. The family tendency is usually more marked when carcinoma occurs in both maternal and paternal lines.

5. Family susceptibility to carcinoma is shown particularly in the case of carcinoma of the mouth, lip, breast, stomach, intestines and uterus.

6. In a family showing the occurrence of carcinoma in several generations there is a decided tendency for the neoplasm to develop at an earlier age in the members of the youngest generations. In this case the neoplasm often shows an increased malignancy.

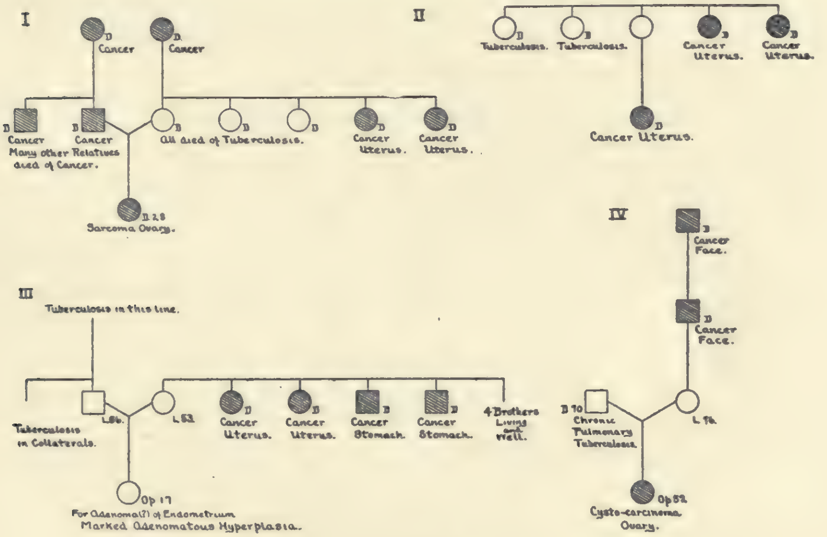

Chart 9

7. Because of the difficulty of obtaining complete family records, the laws of inheritance of carcinoma susceptibility cannot be determined accurately, and it is highly desirable that investigations of large family records should be made relative to the occurrence of carcinoma susceptibility. In Levin's study of cancerous fraternities in connection with the whole family history the percentage of cancerous members in each cancerous fraternity corresponds very closely to the Mendelian percentage of members with recessive unit-characters in a hybrid generation. The same conclusion might be drawn from my cases in certain instances, but it does not seem to me that the data are sufficient for such conclusions. He himself does not consider this conclusion as final. Levin also concludes that resistance to cancer is a dominant character whose absence creates a susceptibility to cancer. While some of my cases show a family history suggesting this, others would indicate a progressive degenerative

inheritance — the running-out of a family line through the gradual development of an inferior stock, particularly as far as resistance to tuberculosis and cancer is concerned.

Levin, as well as Williams,[3] noted the family tendency to specific localization of the cancer, particularly of the uterus in the women, and of the gastro-intestinal tract in the men. This is well shown in my family histories and in some of the cancerous fraternities. Levin concludes that the most important result of his investigation is the fact that it shows the presence of an inherited resistance to cancer growth. I would put it in just the opposite way and say that my observations are important in that they show in certain families an inherited susceptibility to cancer. If the majority of the human race do not show this susceptibility, resistance to cancer is a normal trait of the species. An increased susceptibility becomes, therefore, the abnormal character of importance, and our investigations should be carried along the line of attempting to determine just what lies back of this susceptibility.

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3. Williams: The Natural History of Cancer, 1908, p. 364.

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Age Incidence in Carcinoma

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ANN ARBOR, MICH.

Reprinted from the Archives of Internal Medicine
November, 1913, Vol. 12, pp. 539-545

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AGE INCIDENCE IN CARCINOMA *

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The progressive increase in the incidence of carcinoma as the middle period of life is approached and reached has long been recognized. Most writers have contented themselves with a statement of this fact, leaving the reader to understand that even in advanced years the progressive increase is maintained. For instance, Bashford[1] says: "Carcinoma appears in the human subject with increasing frequency as life advances." He recognizes, however, that the carcinoma incidence in those organs which undergo a definite phase of involution long before senile changes in the organism as a whole are marked, is highest during such involutionary processes. This he bases on statistics of breast and uterine cancer.

Senn[2] gives a suggestion that in extreme old age the cancer incidence is decreased, as the following quotation shows: "Carcinoma manifests a predilection for the conditions incident to senile marasmus, occurring most frequently in persons between 50 and 70 years of age."

It was in the hope of throwing additional light on this and allied problems that the analysis here presented of over 1,100 microscopically verified cases of carcinoma was undertaken.

Several varieties of cancer statistics have been made use of in similar investigations. Such are mortality returns, cancer censuses and hospital and laboratory reports. From the standpoint of a study of age-incidence the first-named fails, in that mortality returns give only the age of the victim when the disease has overpowered him; the cancer census fails in that the report is encumbered with unverified cases; while the greatest objection that can be raised against hospital and laboratory reports is that they are not derived from a representative fraction of the total population.

Our material consists of consecutive cases of carcinoma of known age, diagnosed in the Pathological Laboratory of the University of Michigan between the years 1895 and 1913. This material possesses the following advantages: 1. Every case has been microscopically verified. 2. The age of the patient is obtained at a much earlier stage than in mortality records and thus the actual age-incidence is more nearly represented. 3. The cases are derived from a fairly representative fraction of the total population. The larger part are from the university hospitals, which receive

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* From the Department of Pathology, University of Michigan.

[1] Bashford: Imp. Cancer Research Fund, 1905, No. 2, p. 32.

[2] Senn: Pathology and Surgical Treatment of Tumors, p. 66.

patients from the entire state, and, to a lesser degree, from neighboring states. Because of this fact, and also because they are not charity hospitals, the patients are much more representative of the general population than is ordinarily the case.

The figures for the age distribution of the total population are derived from the United States census report for 1900.[3] This census report was chosen as being more nearly at the midpoint of the period during which the cases occurred than was the census report of 1910. Since more than 90 per cent. of the cases reported are from Michigan, the figures for that state alone were considered. The error here is negligible for the variations in age distribution over a period of a few years, or in neighboring states as compared to Michigan in 1900, are very slight.

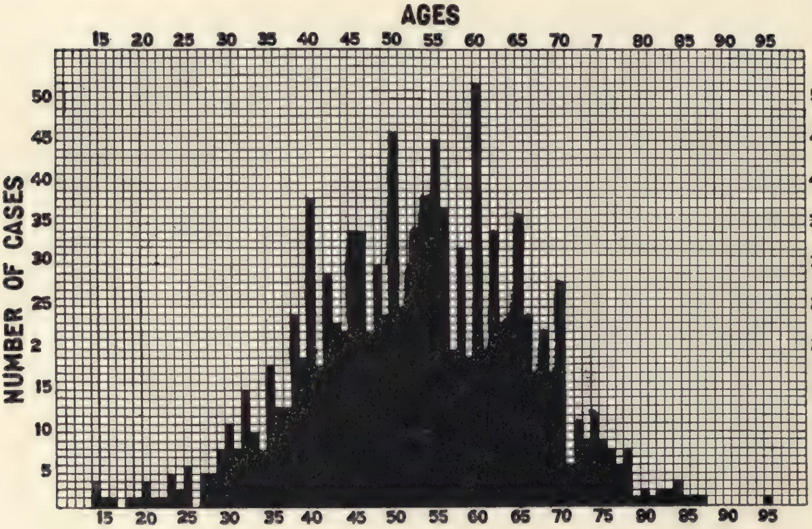

Chart 1

The yearly distribution of the total 1,106 cases is shown by Chart 1. The greatest number for any year is found at the age of 60 with fifty-one cases. The error of approximate answers is well shown by the disproportion in the number of cases for consecutive years. The multiples of five are favored by patients in giving their ages. The even ages show a slight preponderance over the odd. This disproportion is found in some degree in all census statistics.[4] In order to avoid this source of error all analyses have been based on five-year periods having the multiple of five as the middle year in the group. Thus the age period 58 to 62 will presumably represent an accurate grouping of all of the cases given as of age 60, while if the usual quinquennial groups were used, the group 60 to 64 would include many cases which in reality belong in the preceding period.

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[3] Report, Twelfth Census, U. S., 1900, ii, Part 2, 52.

[4] Report, Twelfth Census, U. S., 1900, ii, Part 2, 35.

The percentage of the total population living during each age period and the percentage of the total number of cases of carcinoma for each age period are shown by the two curves of Chart 2. The carcinoma curve lies below the population curve up to age 37. Here the curves cross. At this point the ratio between the two curves is unity, and it may be interpreted as being the point at which the number of cases of carcinoma is the same as it would be were carcinoma uniformly distributed throughout the total population. Beyond this point the ascent of the curve of carcinoma percentages is very rapid and the highest point is reached in the age period 53 to 57.

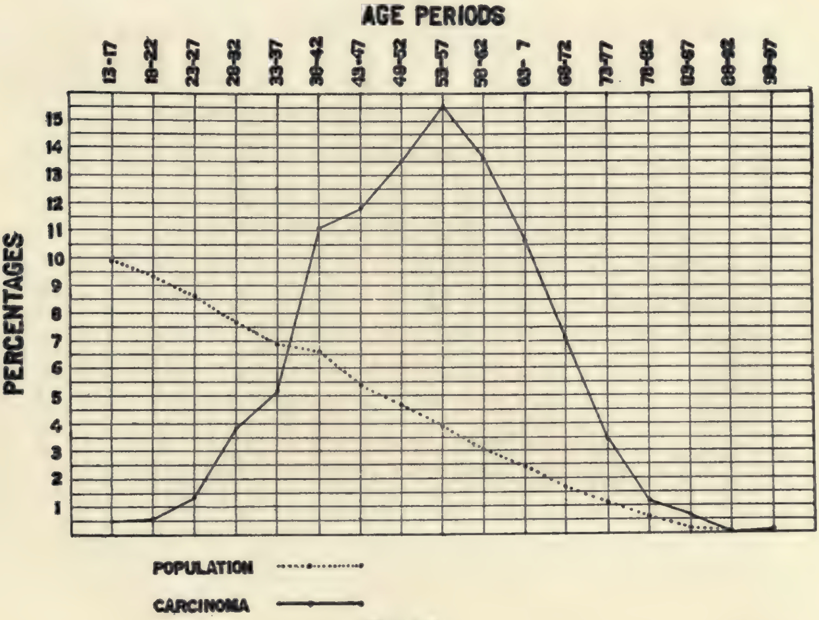

Chart 2

This does not mean that the carcinoma incidence is greatest during this age period, for the decreasing population leaves fewer individuals to be attacked. This point has been further elucidated by computing a series of ratios between the percentages previously used, that is,

$$\text{Ratio for age period N} = \frac{\text{percentage of carcinoma for age period N}}{\text{percentage of population for age period N}}$$

These ratios are plotted in the curve of Chart 3. As previously mentioned, the value is less than one up to age 37 and greater than one thereafter. The apex of the curve is at the age period 58 to 62, and this, therefore, represents the age period of greatest carcinoma incidence.

From 58 to 62 there is a definite fall in the curve, which becomes most marked after 66 to 72. The abrupt rise after 78 to 82 is meaningless, since it is determined by too small a number of cases (eight) to have any value. One must therefore conclude that after 70 years of age there is a decided diminution in the incidence of carcinoma.

Chart 4 shows graphically the age distribution of our cases of carcinoma divided according to sex. The cases in males totaled 495; in females 611. It is noticeable that the curve for female cases rises on the average ten years before that of males, reaches its apex ten years earlier and falls on the average five years ahead of the curve for males. Since, however, the total number of cases differs with the sexes, and the population totals for the sexes are also unlike in their age distribution, no definite conclusions can be drawn from the data presented by Chart 4. It has, therefore, been necessary to construct ratios on the same general plan as before, that is,

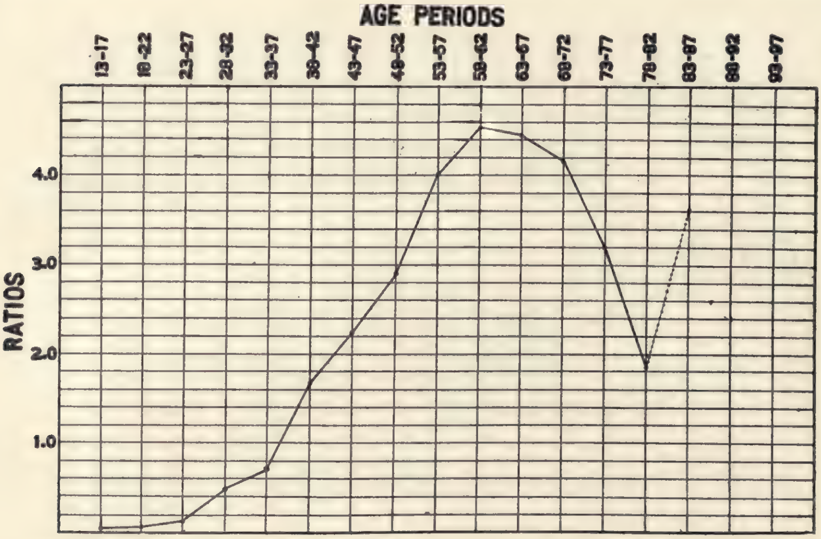

Chart 3

$$\text{Ratio for males, age period N} = \frac{\text{percentage of carcinoma in males at age period N}}{\text{percentage of male population at age period N}}$$

and

$$\text{Ratio for females, age period N} = \frac{\text{percentage of carcinoma in females at age period N}}{\text{percentage of female population at age period N}}$$

By plotting the two series of ratios a graphic representation of the incidence of carcinoma in each sex and at each age period is obtained and a direct comparison is possible (Chart 5). The ratio for females reaches unity about the age 33, while for males this point is not reached until age 39. Among females the incidence of carcinoma reaches its height in

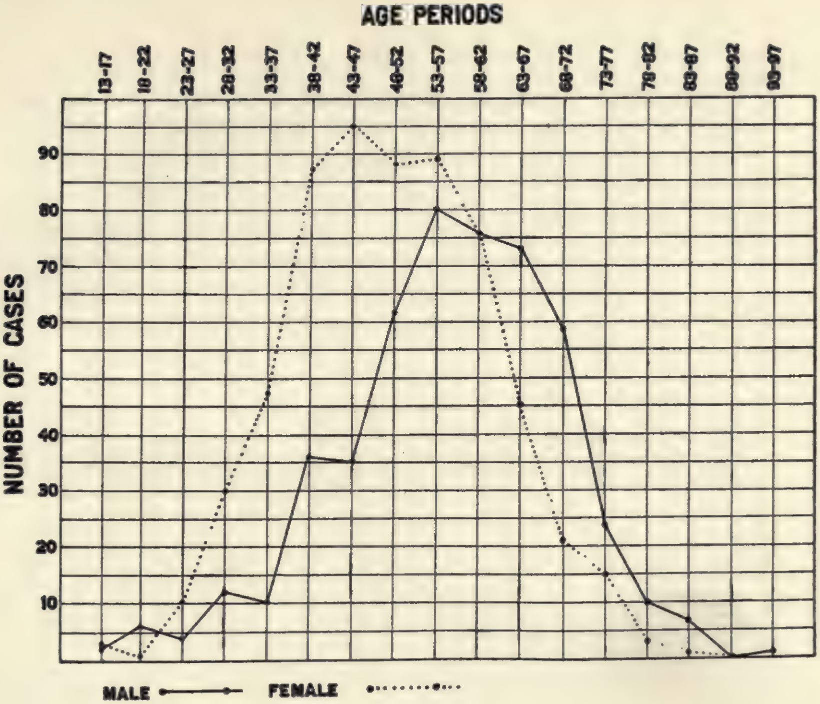

Chart 4

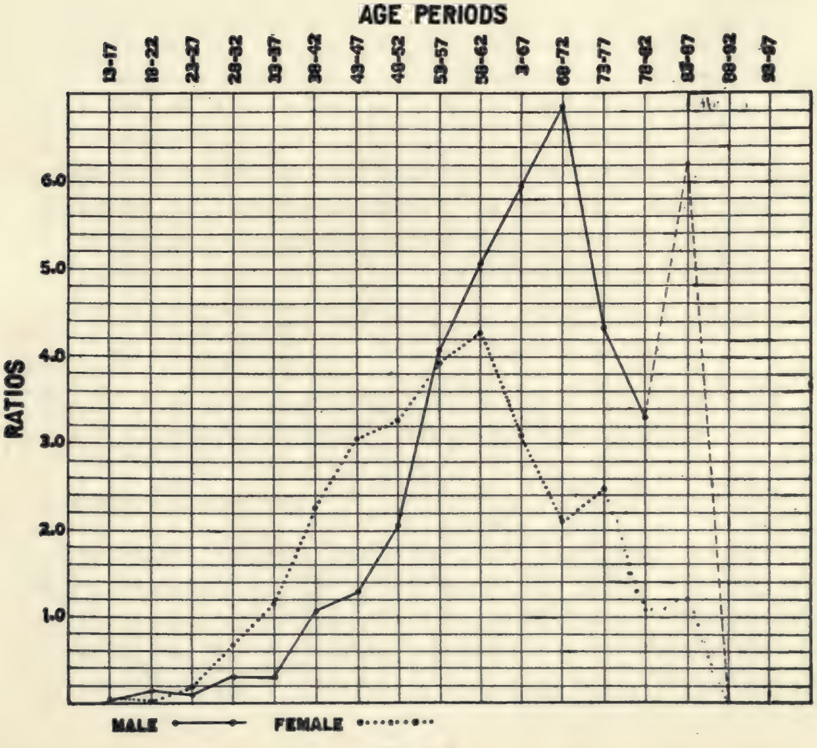

Chart 5

the age period 58 to 62, while carcinoma is most frequently recognized in males at 68 to 72. These latter figures are made somewhat higher than they should be by the cases of basal-celled carcinoma which, occurring most frequently in males, are often diagnosed rather late in life, though they may have been of many years standing. But, even with due allowance for this source of error, it is evident that in the female the wave of carcinoma incidence traverses its cycle five to ten years earlier than in males. The sharp decrease in both curves after the crest of the curve is reached holds good for each sex quite as well as it did in the combined statistics of Chart 3.

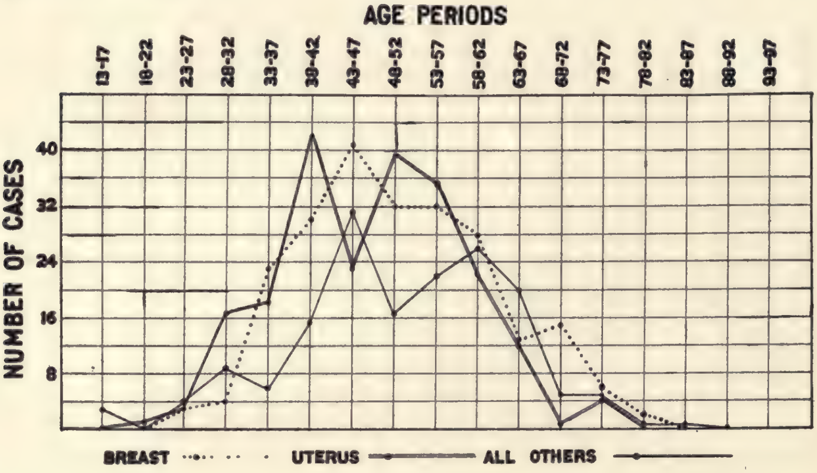

Chart 6

In order to discover what elements in the curve of female cases of carcinoma were responsible for causing it to precede the male curve in all its phases, the female cases were divided into three groups according to the location of the carcinoma.

Breast	229 cases.
Uterus	219 cases.
All others	165 cases.

The age distribution of each of these three types is shown by Chart 6, and in Chart 7 the percentages of the total number of cases in each group occurring during each age period are plotted. It is found that between 33 and 43 the percentages of cases in which carcinoma of the breast and uterus occurs are much higher than that of the group which is designated "all others." These two sources, comprising more than two-thirds of all our cases of carcinoma in women, are therefore very powerful factors in determining the earlier cycle in the general curve for women.

The form of the curves in this chart becomes less regular because of the smaller number of cases being considered. There is one irregularity, however, which while it may be due to the smaller number of cases, may also have a much deeper significance. In the curves which indicate cases in which carcinoma of the uterus occurs, we find:

42 cases, or 19.4 per cent., at age period 38 to 42
23 cases, or 10.6 per cent., at age period 43 to 47.
39 cases, or 18.0 per cent., at age period 48 to 52.

The peculiar drop just at the menopause period, 43 to 47, may find its explanation in the fact that metrorrhagia at this time is usually considered by the patient as but a phenomenon of the climacteric, and therefore unworthy to be investigated.

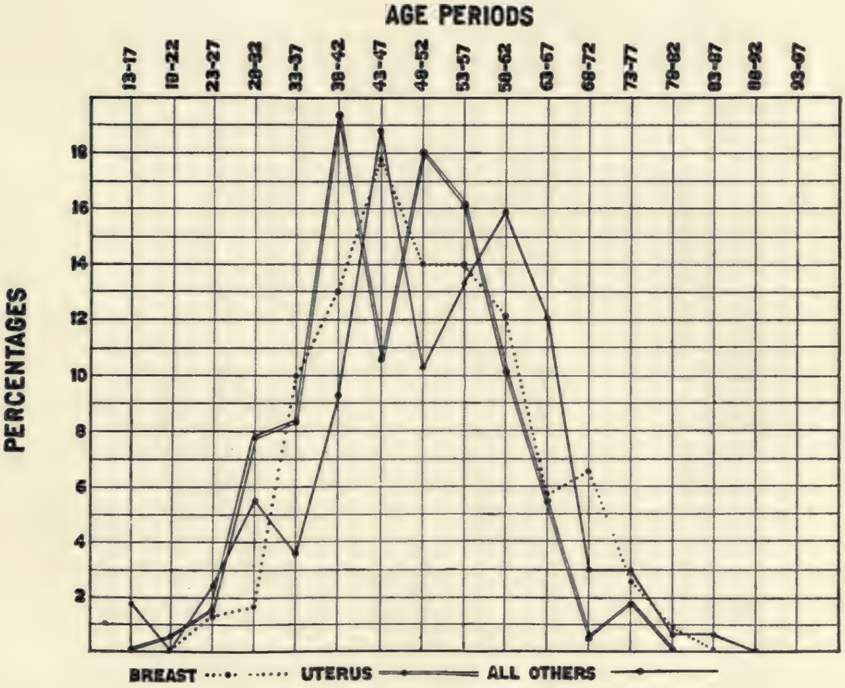

Chart 7

CONCLUSIONS

The analysis here given indicates that:

1. The incidence of carcinoma is greatest at the age period 58 to 62.

2. After this period the carcinoma incidence decreases.

3. Carcinoma incidence in women runs a definite cycle which is roughly parallel to that in men, but precedes it by five to ten years.

4. The earlier age for the phases of the curve for women is largely due to the earlier appearance of carcinoma of the breast and uterus as compared to other varieties of carcinoma.

Primary Carcinoma of the Larger Bronchi

An Analysis of Ninety Cases with Regard to Pathology, Symptomatology and Diagnosis; and Report of New Case

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Reprinted from the Archives of Internal Medicine
March, 1913, Vol. 11, pp. 314-333

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CHICAGO
American Medical Association
Five Hundred and Thirty-Five North Dearborn Street
1913

PRIMARY CARCINOMA OF THE LARGER BRONCHI

AN ANALYSIS OF NINETY CASES WITH REGARD TO PATHOLOGY, SYMPTOMATOLOGY AND DIAGNOSIS; AND REPORT OF A NEW CASE*

CARL VERNON WELLER, A.B.
ANN ARBOR

The large number of case reports of lung and bronchial neoplasms which have appeared in the literature in the last two years gives evidence of a renewed interest in this subject. Two factors have served to draw attention to its importance. There has been a growing realization of the fact that bronchial and pulmonary carcinomata are by no means as rare as was once thought, and the developing possibilities of intrathoracic surgery have made their early diagnosis a matter of more than scientific curiosity. It is hoped that the analysis of a large number of carefully selected cases of primary carcinoma of the larger bronchi will aid in forming a definite clinical picture for this condition and in taking it out of the mixed group of lung and bronchial neoplasms in which it has usually been considered. Even Adler,[1] who has written the most extensive of the recent monographs on the subject, does not attempt to separate the two types in his list of cases.

Several attempts have been made to collect from the literature the cases of primary carcinoma of the lungs and bronchi. Reinhard[2] found 25 cases in 1878, Wolf[3] 31 cases in 1895, and Adler[1] 374 cases in 1911. These authors, however, admitted to their lists cases without microscopical verification of their carcinomatous nature. In 1891, Werner[4] could find but nine cases fully verified, while in 1896 Pässler[5] listed about 70 such. In differentiating between carcinoma and sarcoma, in ruling out tuberculous processes, and especially in examining metastases and considering the possibility of a primary growth elsewhere, microscopical examinations become necessary, and a statistical study loses in value in proportion as it includes unverified cases.

Wolf[2] separated the cases which he listed into those primary in the lung parenchyma and those having their origin from the larger bronchi.

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*Manuscript submitted for publication in THE ARCHIVES Jan. 21, 1913.

*From the Pathological Laboratory of the University of Michigan, Ann Arbor, Michigan.

1. Adler, J.: Primary Malignant Growths of the Lungs and Bronchi, 1911.
2. Reinhard, W.: Arch. d. Heilk., 1878, xix, 369.
3. Wolf, K.: Fortschr. d. Med., Berlin, 1895, xiii, 725.
4. Werner, M.: Das primäre Lungencarcinom. Dissert., Freiburg, 1891.
5. Pässler, H.: Arch. f. path. Anat., Berlin, 1896, cxlv, 191.

He placed twenty-three of his thirty-one cases in the second group. It is often found impossible to determine even roughly the point of origin of the growth, because of the enormous size of the neoplasm and the widespread involvement of surrounding structures, but there is a large group in which the bronchial origin may be established. Obviously the symptomatology of these cases differs very much from that of cases in which the neoplasm is located in the peripheral portions of the bronchial tree. This difference has been referred to by Pässler,[5] but he does not group the cases accordingly in compiling his clinical statistics.

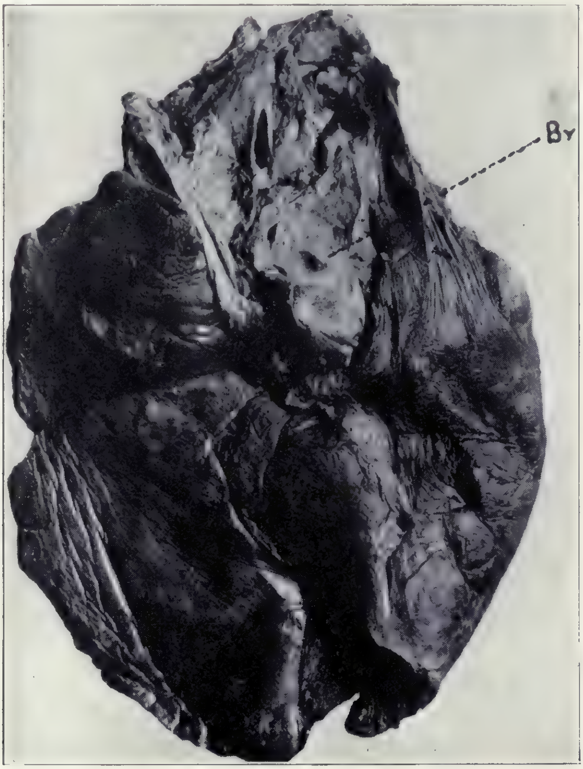

Fig. 1.—Right lung showing right main bronchus (Br.) cut across. Its lumen is much reduced by the surrounding carcinomatous infiltration.

It is the purpose of this study to collect the authenticated cases of primary carcinoma of the larger bronchi and investigate the pathological and clinical features of this group. Only those cases meeting the following requirements have been admitted:

1. An autopsy must have been performed.
2. The carcinomatous nature must have been verified microscopically.
3. There must be no reasonable suspicion that the neoplasm is not a primary growth.

4. There must be good evidence of bronchial origin. This may be found either in the gross relationship of the tumor to a bronchus or in the microscopical relationship of the neoplasm to bronchial elements.

As far as possible the following list has been made to include all cases meeting the above tests. The original reports have been used wherever access could be had to them, but full acknowledgment is made of data from Adler's recent monograph[1] in regard to twenty cases in which the original sources were not obtainable. It has also been possible to include nineteen cases which are not found in his somewhat earlier compilation. Beyond a doubt there are many other cases of bronchial carcinoma in the literature, but they cannot find a place here because they fail to meet one or more of the criteria previously mentioned.

SYNOPSIS OF REPORTED CASES

1. ALLAN.[6] 1907, M., 38. Pain in left chest and arm; dyspnea; palpable tumor at origin of left sternomastoid; left pupil contracted, ptosis of left lid, left vocal cord fixed in cadaveric position. Left main bronchus blocked by encircling tumor mass of scirrhous type, with large masses of cells; metastases in bronchial nodes and left lobe of thyroid.

2. BECK.[7] 1884, M., 65. Blacksmith. Alveolar carcinoma of right main bronchus and its branches. Lumina constricted; cavity in right upper lobe; secondaries in right bronchial nodes, mediastinal pleura, thyroid, liver, both adrenals; superior vena cava involved and thrombosed; origin from mucous glands.

3. BECK.[7] 1884., F., 57, charwoman. Primary alveolar carcinoma of right main bronchus and its chief branches; polyhedral cells; bronchial nodes at hilus secondarily involved; stenosis of superior vena cava; origin from bronchial mucous glands.

4. BOECKER.[8] 1910, F., 83, housewife. Tumor mass reaching from hilus to pleura in right lower lobe; situated about two medium sized bronchi; alveolar in structure with mucus formation; secondaries in tracheal and cervical nodes (?) not microscopically examined.

5. BOYD.[9] 1887. M., 38. Bottle-blower. Cough, dyspnea, cyanosis, blood-tinged sputum, veins of forehead and neck dilated; edema of right arm and face; voice hoarse and aphonic; carcinoma extending to the right from region of bifurcation and compressing vena cava.

6. DELORME [10] (After Adler). 1901, M., 25. Cough, fever, blood tinged sputum; dilated veins; paralytic symptoms; secondary nodules; cylindric celled carcinoma of left chief bronchus; secondaries in pericardium, pleura, skull, suprarenals, liver, various long bones, sternum, ribs and lymph-nodes.

7. DAVIS AND LE COUNT.[11] 1908. M., 58. Saloonkeeper. Cough, blood-streaked sputum; glandular masses in neck and axilla; dulness and increased fremitus over upper left; hoarseness, dyspnea, cyanosis; paralysis of left vocal cord; carcinoma of left main bronchus, in part adenomatous with mucin-like content; origin from mucous glands.

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6. Allan, G. A.: Lancet, London, 1907, ii, 961.

7. Beck: Ztschr. f. Heilk., 1884, v.

8. Boecker, E.: Zur Kenntniss der primären Lungenkarzinome. Inaug. Dissert., Berlin, 1910.

9. Boyd: Lancet, London, 1887, ii, 60.

10. Delorme: Ueber primäres Lungencarcinom. Dissert., Jena, 1901.

11. Davis and Le Count: Chicago Path. Soc., 1908, vii, No. 5.

8. Davis and Le Count.[11] 1908. F., 32. Dyspnea, cough, blood-stained sputum, hoarseness; left chest fixed and bulging; mucosa of chief bronchi resembled skin; left main bronchus almost occluded by squamous-celled carcinoma; left lung airless; metastases in tracheal and retro-aortic nodes, pleura, liver, both adrenals, both kidneys and both ovaries.

9. Dömeny.[12] 1902. M. Sharp pain in left side; cough with scanty sputum; medullary carcinoma of bronchus to left lower lobe; atelectasis of that lobe; emphysema of right lung; secondaries in lymph-nodes and right kidney; origin from bronchial epithelium.

10. Dömeny.[12] 1902. F., 79. Right hydrothorax; carcinoma of left main bronchus; branch to lower lobe nearly obstructed; large nests of polygonal cells; secondaries in bronchial nodes.

11. Dömeny.[12] 1902. M., 41. Pain in head, auditory and visual disturbances; choked disk on both sides; cylindric celled adenocarcinoma of bronchus to left lower lobe; that lobe atelectatic; seven brain metastases; origin from mucous glands.

12. Dömeny.[12] 1902. F., 66. Fever, cough, pain in right side, dyspnea; dulness below angle of scapula on the right; cylindric celled adenocarcinoma of bronchus to upper right lobe; secondaries in bronchial and mediastinal nodes; origin from mucous glands.

13. Dömeny.[12] 1902. M., 29. Pain in left arm; tumor masses on ribs, sternum and cranium; adenocarcinoma of bronchus to left lower lobe; secondaries of cranium, ribs, sternum, liver, retrobronchial and retroperitoneal nodes, brain, right kidney; much mucus formation, especially in metastases; origin from mucous glands.

14. Dorsch.[13] 1886 (After Pässler). F., 54. Two medullary masses in right upper lobe, growing from right chief bronchus and involving pericardium and vena cava; the latter thrombosed; large polymorphous cells; metastases in lymph-nodes at hilus, lung tissue of same side, liver, spleen, kidneys, sternum, dura mater.

15. Ehrich.[14] (After Adler). 1891. M., 51. Dulness over upper right; hemoptysis; cancerous tissue in sputum; large node in right axilla; alveolar carcinoma of right main bronchus; polymorphous cells; secondaries in pericardium, chest wall, bronchial nodes and diaphragm; origin from mucous glands.

16. Ehrich[14] (After Adler). 1891. F., 56. Clinical diagnosis, tumor of mediastinum; alveolar carcinoma of lower trachea, right chief bronchus and its branches; polymorphous cells; right lung atelectatic; metastases in bronchial and mediastinal lymph-nodes, left lung, liver, heart.

17. Ernst.[15] 1896. M., 50. Cerebral symptoms, cough and mucopurulent sputum; bronchus to right upper lobe occluded by papilliferous growth; squamous-celled carcinoma; metastases in left adrenal, cerebrum and cerebellum.

18. Fränkel.[16] 1904. M., 52. Laborer. Pain in left chest; cough; blood-stained sputum; enlarged inguinal gland found to be carcinomatous; occlusion of left main bronchus by cylindric celled carcinoma; secondaries in inguinal and tracheal nodes.

19. Fränkel.[16] M., 40. Chill, high fever, dyspnea; mucopurulent sputum, later dirty brown; bronchus to right lower lobe nearly occluded by a cylindric-celled carcinoma; bronchiectasis; secondary involvement of nodes at hilus.

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[12] Dömeny: Ztschr. f. Heilk., Wien, 1902, xxiii, 407.

[13] Dorsch: Ein Fall von primären Lungenkrebs, Inaug. Dissert., Tübingen, 1886.

[14] Ehrich: Ueber das primäre Bronchial- und Lungencarcinom. Dissert., Marburg, 1891.

[15] Ernst, P.: Beitr. z. path. Anat., etc., Jena, 1896, xx, 155.

[16] Fränkel, A.: Spezielle Pathologie u. Therapie der Lungenkrankheiten, 1904.

20. **Friedlander**[17] (after Püssler). 1885. M. White medullary mass proceeding from left upper lobe bronchus; no metastases; squamous-celled carcinoma with epithelial pearls.

21. **Garbat.**[18] 1909. M., 64. Insurance agent. Asthenia, emaciation, cough, blood-stained sputum, night sweats; tumor mass over right scapula found to be carcinoma; central portion of right lung involved in mass of carcinomatous growth with mucus-containing alveoli; origin from mucous glands; secondaries in liver, both lungs, bronchial, supraclavicular and retroperitoneal nodes; old tuberculosis of left apex.

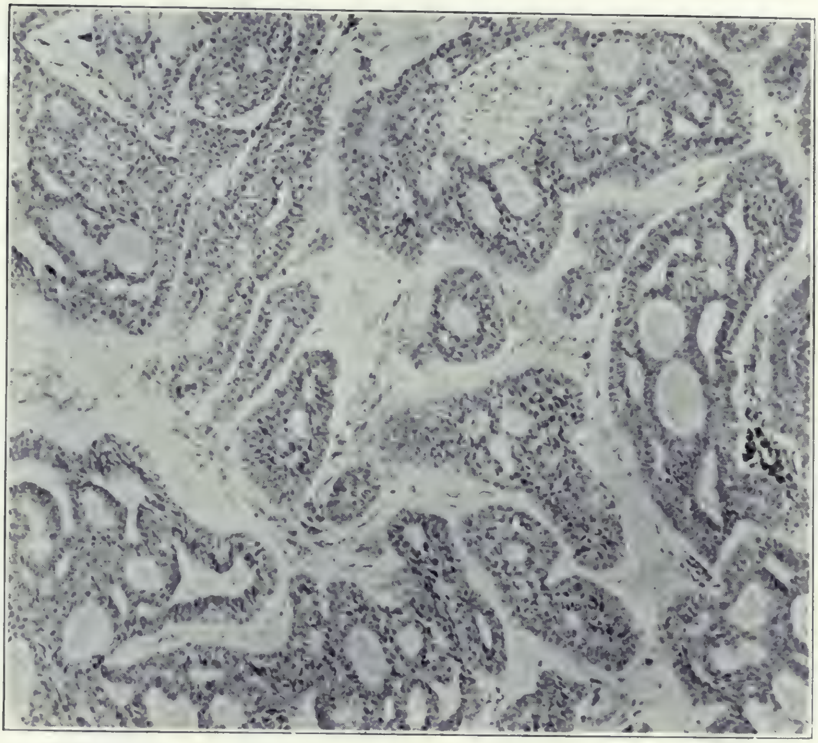

Fig. 2.—Section from the bronchial adenocarcinoma shown in Fig. 1. The alveolar spaces are filled with mucin. Zeiss obj. "B."

22. **Georgi.**[19] 1879. M., 60. Blacksmith. History of trauma; cough developed with scanty sputum becoming bloody; died one year later; medullary carcinoma at hilus of left lung; bronchiectasis; upper left lung atelectatic; right emphysematous; no metastases.

23. **Geipel.**[20] 1899. M., 70. Cigar-maker. Symptoms of some severe pulmonary disease; upper main branch of left chief bronchus almost occluded by an alveolar cylindric celled carcinoma; secondaries in left lower lobe; origin from bronchial mucosa.

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17. Friedlander: Fortschr. d. med., 1885, i, 307.
18. Garbat, A. L.: Am. Jour. Med. Sc., 1909, N. S., cxxxvii, 857.
19. Georgi: Berl. klin. Wchnschr., 1879, xxviii and xxix.
20. Geipel: Centralbl. f. Allg. Path. u. path. Anat., 1899, x, 848.

24. **Gougerot.**[21] 1905. M., 46. Old tuberculosis; dyspnea, cough, mucopurulent sputum with Koch bacilli; dulness in upper right; polyuria; right main bronchus obstructed by growth which extended throughout upper portion of lung; squamous celled carcinoma with pearls; metastases in peribronchial nodes and left kidney.

25. **Hall and Tribe.**[22] 1905. M., 17. Cough, dyspnea, cachexia; blood-tinged sputum; glycosuria; columnar-celled carcinoma of bronchus to left lower lobe; secondaries in upper left lobe, liver, retroperitoneal and cervical nodes and calvarium.

26. **Hampeln.**[23] 1897. M., 57. Chronic bronchial catarrh, emphysema, asthenia; bloody expectoration; dyspnea; primary bronchial carcinoma with polymorphous cells, origin from mucous glands; no metastases.

27. **Handford.**[24] 1888. M., 64. Collier. Cough, dyspnea, rapid wasting; history of trauma received five months previously; blood-stained sputum; dulness over upper left thorax; growth beginning three-quarters of an inch above tracheal bifurcation and extending along left chief bronchus, nearly filling lumen; secondaries in left lung, pleura and liver; origin from bronchial mucosa; right lung emphysematous.

28. **Handford.**[25] 1889. M., 63. Pain after taking food, cough, vomiting, weakness; no dulness; medullary carcinoma completely occluding lower primary division of left bronchus; left lower lobe collapsed; secondaries in liver and bronchial nodes; stomach symptoms due to ulcer.

29. **Henrici.**[26] 1912. M., 62. Cough, bloody sputum; flatness on right between clavicle and fourth rib; squamous celled carcinoma of bronchus to right upper lobe; origin from bronchial mucosa.

30. **Hinterstoissen.**[27] 1889. M., 59. Lieutenant-colonel. History of trauma; glandular swelling of left side of neck and right axilla; pain in left arm; tumor of right ring finger was found to be carcinoma; paralysis of left vocal cord; sputum often bloody and diagnosis made from cells in sputum; carcinoma simplex involving bifurcation and both main bronchi; secondaries in right axillary, left supraclavicular, bronchial and mediastinal nodes and terminal phalanx of right ring finger.

31. **Hitz**[28] (after Adler). 1887. F., 40. Fever, cough, dyspnea, dysphagia, bloody sputum; alveolar carcinoma of right main bronchus; bronchiectasis of right lung, emphysema of left; secondaries in regionary lymph-nodes.

32. **Horn.**[29] 1907. F., 18. Cough, dyspnea, pain in left thorax, hemoptysis; sudden death; left lung atelectatic; bronchiectasis; left main bronchus completely occluded by carcinoma of glandular structure; spaces contained colloid-like material; origin from bronchial mucosa.

33. **Japha**[30] (after Adler). 1892. M., 48. Dyspnea, pain, cyanosis, pleural effusion; dilated veins over thorax; bloody sputum with cancerous particles; cylindric and squamous celled carcinoma developing from hilus along right bronchial tree; metastases in lymph-nodes, pleura and pericardium; origin from bronchial mucosa.

34. **Karrenstein**[31] (after Adler). 1908. M., 48. Hemoptysis; pain in right chest; dulness over right lung; bronchoscope showed tumor in right bronchus;

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[21] Gougerot, H.: Bull. et mém. Soc. anat. de Par., 1905, lxxx, 294.

[22] Hall and Tribe: Lancet, London, 1905, i.

[23] Hampeln, P.: Ztschr. f. klin. Med., Berlin, 1897, xxxii, 247.

[24] Handford, H.: Tr. London Path. Soc., 1888-9, xl, 40.

[25] Handford, H.: Tr. London Path. Soc., 1889-90, xli, 37.

[26] Henrici: Jour. Med. Research, 1912, xxvi, 395.

[27] Hinterstoissen, H.: Wien. klin. Wchnschr., 1889, ii, 374.

[28] Hitz: Ein Beitr. z. Casuistik des primären Lungencarcinoms. Dissert., Zurich, 1887.

[29] Horn, O.: Virchows Arch. f. path. Anat., 1907, clxxxix, 414.

[30] Japha: Ulcer primären Lungenkrebs. Dissert., Berlin, 1892.

[31] Karrenstein: Charité Ann., 1908, xxxii, 315.

squamous celled carcinoma with pearls; metastases in liver, stomach, kidneys, brain (?) and pericardium; origin from bronchial mucosa.

35. KIDD.[32] 1892. M., 52. Butcher. Cough for twelve months; pain in left side, blood-streaked sputum, dyspnea, dulness and feeble breath sounds on left; tumor at bifurcation and along left chief bronchus and branch to upper lobe; bronchiectasis; atelectasis on left; secondaries in adrenal and jejunum (?).

36. KLÜBER[33] (after Adler). 1898. F., 34. Apparently healthy, sudden death following burn; glandular carcinoma with small cuboidal cells completely obstructing right lower main bronchus; bronchiectasis in right lower lobe; no metastases; origin from mucous glands.

37. KOERNER.[34] 1888. M., 64. Money loaner. Cough, bloody sputum; flatness and absent fremitus on right; severe dyspnea; right lung emphysematous; carcinoma occluding right chief bronchus.

38. KRETSCHMER[35] (after Adler). 1904. M., 54. Clinical diagnosis: purulent bronchitis, bronchiectasis, pleurisy, diabetes; alveolar carcinoma of left lower bronchus; no metastases; origin from mucous glands.

39. KRETSCHMER[35] (after Adler). 1904. M., 68. Left-sided pleural effusion; adenomatous carcinoma of left main bronchus; metastases in bronchial, mediastinal, retroperitoneal nodes, left kidney, liver, both adrenals. Origin from mucous glands.

40. KUBR.[36] 1906. M., 36. Pain in chest, cough, dyspnea, loss of weight and strength. Cylindric celled carcinoma arising from mucosa of trachea and bronchi, proliferating along bronchial ramifications and obstructing lumina; diagnosed from metastases.

41. LANGHANS.[37] 1871. M., 40. Symptoms of right bronchial stenosis; died suddenly in a "suffocative attack"; alveolar carcinoma at tracheal bifurcation and along wall of right bronchus; small polyhedral cells; no secondaries; origin from mucous glands.

42. LARDILLON[38] (after Adler). 1903. M., 60. Cough, emaciation, asthenia, mucopurulent sputum; alveolar carcinoma of left main bronchus; polymorphous cells; bronchiectasis and atelectasis of left lung; secondaries in nodes at left hilus.

43. LETULLE AND BIENVENUE[39] (after Adler). 1908. F., 63. Emaciation, hoarseness, dyspnea, blood-stained sputum; alveolar carcinoma of left main bronchus; polymorphous cells; secondaries in tracheal and bronchial nodes and adrenals; origin from bronchial mucosa.

44. MAUN[40] (after Adler). 1905. M., 50. Asthenia; abundant hemoptysis; alveolar carcinoma of left main bronchus; secondaries in bronchial nodes, pericardium, left ventricle; origin from bronchial mucosa.

45. MCINTYRE.[41] 1912. N., 67. Dyspnea, cough, bloody sputum; dulness over upper left; adenocarcinoma of bronchus to upper left lobe; no metastases; tuberculosis also present.

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32. Kidd, P.: Tr. Clin. Soc. London, 1892, xxv, 178.

33. Klüber: Ein Fall von Bronchialcarcinom und Lungencyste. Dissert., Erlangen, 1898.

34. Koerner, O.: München. med. Wchnschr., 1888, xxxv, 178.

35. Kretschmer: Ueber das primäre Bronchial- und Lungenkarzinom. Dissert., Leipzig, 1904.

36. Kubr: Centralbl. f. inn. Med., 1906, No. 44, p. 1089.

37. Langhans: Virchows Arch. f. path. Anat., xliii, 470.

38. Lardillon: Contribution à l'étude du cancer des poumons. Thèse de Lyon, 1903.

39. Letulle et Bienvenue: Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, xxv, Series 3, p. 610.

40. Maun, J.: Deutsch med. Ztschr., 1905, xxvi, 537.

41. McIntyre: Glasgow Med. Jour., 1912, lxxviii, 95.

46. Merklen and Girard[42] (after Adler). 1901. M., 45. Dyspnea, dysphagia, aphonia; dulness over right lung; blood-streaked sputum; alveolar carcinoma of right main bronchus; no metastases.

47. Meunier.[43] 1895. M., 70. Cabinet maker. Extreme dyspnea for eight days; semi-stuporous; cough; sputum blood-tinged; healed tubercles in left apex; tumor mass at hilus of right lung; alveolar structure, polyhedral cells; origin from bronchial glands.

48. Minssen[44] (after Adler). 1900. M., 43. Pain in right chest, cough, dyspnea, bloody sputum; alveolar carcinoma of right lower lobe bronchus; some mucus formation in neoplasm; secondaries in left pleura, bronchial and retroperitoneal nodes; pancreas, spleen, kidneys; origin from mucous glands.

49. Ogle.[45] 1893. F., 48. Left bronchus completely obstructed by polypoid growth near bifurcation; purulent material in bronchi; alveolar carcinoma; metastases in bronchial nodes.

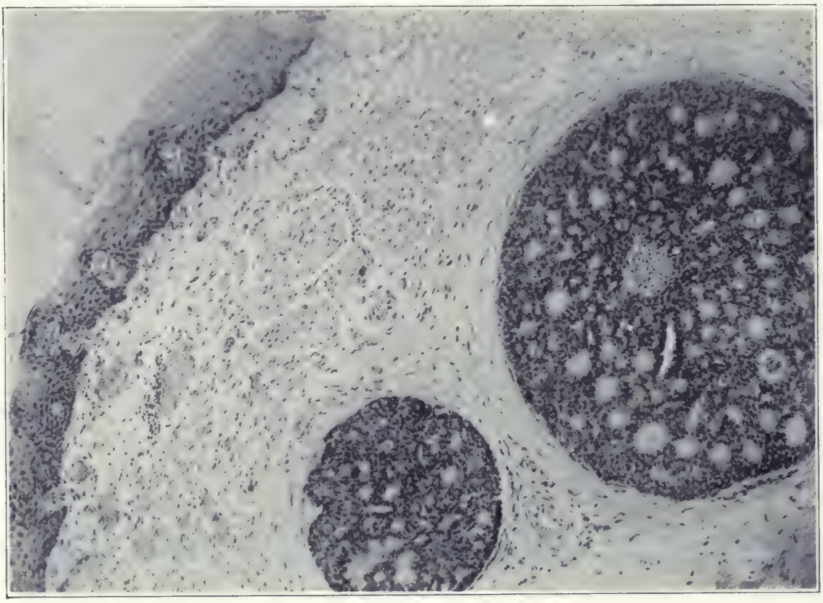

Fig. 3.—Wall of esophagus showing ingrowth of bronchial adenocarcinoma by direct extension. Zeiss obj. "B."

50. Packard.[46] 1905. M., 55. Cigarmaker. Cough, dyspnea, bloody sputum; dilated veins over thorax and flatness over entire right, with absent fremitus; enlarged abdomen; lymph-nodes in both axillae. Death from hemorrhage. Squamous celled carcinoma involving all of right main bronchus and part of left; secondaries in left lung and pleural surface of diaphragm.

51. Pässler.[5] 1896. M., 73. Pensioned policeman. Cough and sputum, never bloody; left recurrent laryngeal paralysis; medullary cylindric celled carcinoma

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42. Merklen and Girard: Bull. et mém. Soc. méd. d. hôp. de Paris, 1901, xviii, Series 3, p. 760.

43. Meunier, H.: Arch. gén. de méd., Par., 1895, i, 343.

44. Minssen: Ueber primären Lungenkrebs. Dissert., Kiel, 1900.

45. Ogle, C.: Tr. London Path. Soc., 1893-4, xlv, 25.

46. Packard, M.: Med. News, New York, 1905, lxxxvi, 303.

of left chief bronchus, compressing trachea; bronchiectasis in left lung, emphysema in right; secondaries in both kidneys.

52. PÄSSLER.[5] 1896. M., 52. Chronic laryngitis; repeated hemorrhages; small ulcerating squamous-celled carcinoma of right main bronchus; fatal hemorrhage from erosion of right pulmonary artery.

53. PÄSSLER.[5] 1896. M., 63. Nearly complete right sided hemiplegia; cachexia. Carcinoma of bronchus in left lower lobe; metastases in right lower lobe, liver, cerebrum and cerebellum; cylindric cell type with some mucous degeneration.

54. PAROW[47] (after Adler). 1896. M., 62. Dyspnea, cachexia, dysphagia. Tumor in right supraclavicular region; cylindric and polymorphous celled carcinoma of right main bronchus and first portion of left; metastases in cervical and supraclavicular nodes. Origin from bronchial mucosa.

55. PEABODY.[48] 1891. M., 33. Stevedore. Cough, mucoid expectoration, pain in left chest; impaired resonance over left, hyperresonance over right side; tumor mass 2¾ inches in diameter in and around left chief bronchus; metastases in lungs.

56. PERITZ[49] (after Adler). 1896. M., 48. Pain in right chest, cough, dyspnea, cachexia; flatness over entire right; bloody sputum; enlarged axillary and cervical nodes; alveolar cylindric celled carcinoma of right main bronchus; secondaries in mediastinal, mesenteric, axillary and cervical nodes, and liver. Origin from ducts of mucous glands.

57. PITT.[50] 1887. F., 67. Dyspnea; lessened motility of right chest; right main bronchus almost occluded by surrounding growth; bronchiectasis of right lung. Carcinoma of a glandular scirrhous type; metastases in left lung and right supraclavicular nodes.

58. REINHARD.[1] 1878. M., 47. Varnisher. Hoarseness, dyspnea, cyanosis, swelling of face and neck; pain in chest. Alveolar carcinoma of bronchus to right upper lobe, compressing superior vena cava; left lung emphysematous. Origin from mucous glands (?).

59. ROSENTHAL[51] (after Adler). 1899. F., 52. Hemiplegia and other cerebral symptoms; some cough and dyspnea. Alveolar cylindric celled carcinoma of left main bronchus; secondaries in brain, bronchial and tracheal nodes and left ventricle.

60. SCHRÖTTER[52] (after Nager). 1907. F., 57. Paralysis of left recurrent laryngeal. Squamous celled carcinoma at bifurcation of trachea completely blocking left chief bronchus.

61. SEHRT[53] (after Adler). 1904. M., 66. Alveolar squamous celled carcinoma of right main bronchus. Secondaries in bronchial and tracheal nodes; bronchiectasis; chronic tuberculosis; fatal hemorrhage following erosion of pulmonary artery.

62. SEHRT[53] (after Adler). 1904. M., 68. Dyspnea, dulness over left chest, hemoptysis. Squamous celled carcinoma of left main bronchus; secondaries in bronchial lymph-nodes and esophagus; chronic tuberculosis.

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47. Parow: Ein Fall von primären Lungencarcinom. Dissert., Greifswald, 1896.

48. Peabody, G. L.: Med. Rec., New York, 1891, xxxix, 438.

49. Peritz: Ueber Brusthöhlen Geschwülste. Dissert., Berlin, 1896.

50. Pitt, G. N.: Tr. London Path. Soc., 1887-8, xxxix, 54.

51. Rosenthal: Ueber einen Fall von primären Lungencarcinom. Dissert. München, 1899.

52. Schrötter: Klinik der Bronchoskopie, 1907. Quoted by F. R. Nager in Arch. f. Laryngol. u. Rhinol., Berlin, 1907, xx, 275.

53. Sehrt: Beiträge zur Kenntniss des primären Lungencarcinoms. Dissert. Leipzig, 1904.

63. Stieb[54] (after Adler). 1900. M., 50. Patient died of cirrhosis of liver. Submucous squamous-celled carcinoma of bronchus to left lower lobe; secondaries in regionary lymph-nodes.

64. Stieb[54] (after Adler). 1900. M., 60. Cough, pain, weakness. Alveolar squamous-celled carcinoma at bifurcation of right main bronchus; secondaries in both lungs and supraclavicular nodes.

65. Stilling.[55] 1881. M., 52. Alveolar carcinoma of bronchus to right middle lobe; large polygonal cells; metastases in bronchial, mediastinal and cervical nodes, pericardium and liver.

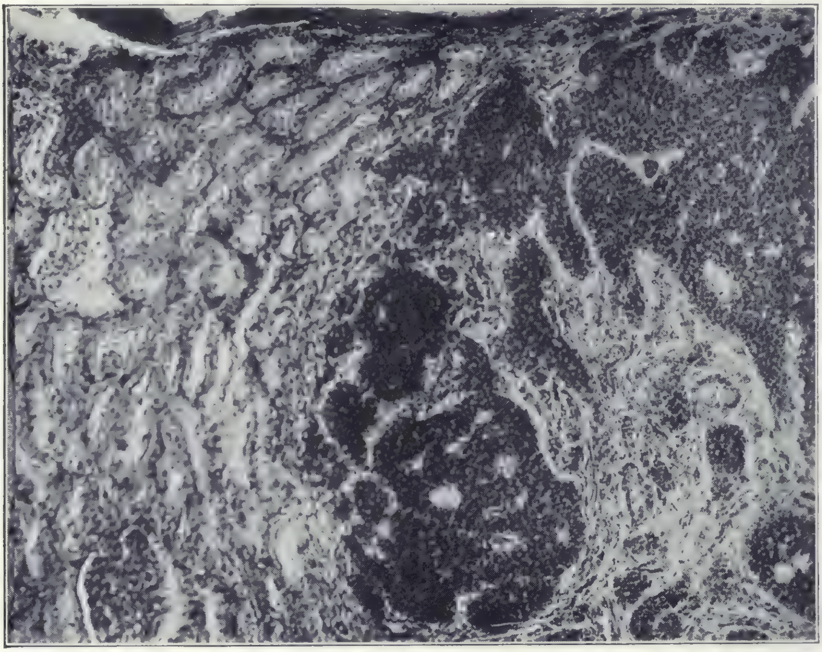

Fig. 4.—Metastatic growth in kidney from primary bronchial adenocarcinoma. The mucus formation is still present but not as marked as in the primary growth. Zeiss obj. "B."

66. Stropeni.[56] 1910. F., 35. Housekeeper. Pain in side, back and shoulder; cough; sputum blood-streaked. Subcutaneous carcinomatous nodule of left arm; fracture of left femur; left lung atelectatic; right lung emphysematous. Adenocarcinoma from mucous glands of left chief bronchus; secondaries in both lungs, epicardium, liver, both kidneys, spleen, right femur, thoracic and lumbar vertebrae and cranial vault.

67. Turnbull and Worthington[57] (after Adler). 1908. M., 56. Symptoms mainly referable to cord lesion. Mucus secreting carcinoma of bronchus to right lower lobe; secondaries in seventh and eighth dorsal vertebrae and in ribs.

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54. Stieb: Ueber das Plattenepithelcarcinom der Bronchien. Dissert. Giessen, 1900.

55. Stilling: Virchows Arch. f. path. Anat., 1881, lxxxiii, 77.

56. Stropeni, L.: Ztschr. f. Krebsforsch., Berlin, 1910, ix, 1-21.

57. Turnbull and Worthington: Arch. Path. Inst. London Hosp., 1908, ii, 163.

68. SCHRÖTTER.[58] 1907. M., 44. Cough and stabbing pain in right side; dilated veins on left chest, abdomen and arm; bloody sputum. Specimen from right main bronchus was found to be squamous-celled carcinoma with glycogen-containing cells; tuberculosis in right apex; emphysema of left lung.

69. WAGNER.[59] 1903. Cylindric celled carcinoma of left chief bronchus. Lumen of bronchus obstructed by cauliflower growth; metastases in left lung, anterior mediastinum, left lobe of liver. Origin from bronchial mucosa.

70. WATSUJI.[60] M., 56. Mucosa reddened and broken at origin of left chief bronchus. Near hilus a large tumor mass completely infiltrating bronchial wall; right lung emphysematous; squamous-celled carcinoma. Origin from bronchial mucosa.

71. WATSUJI.[60] 1904. M., 60. No clinical history. Squamous-celled carcinoma of left chief bronchus; metastasis in a bronchial node which also contained a caseating tubercle.

72. WATSUJI.[60] 1904. M., 59. Squamous-celled carcinoma of right lower lobe bronchus; right lung atelectatic; patient was also tuberculous.

73. WATSUJI.[60] 1904. Microscopical report without history or protocol; sections showed change of epithelium of a lower lobe bronchus into squamous type; wide peripheral extension from this bronchus.

74. WATSUJI.[60] 1904. M., 64. Tumor mass at point of division of bronchus to middle lobe; squamous-cell type with hyaline pearls.

75. WEINBERGER.[61] 1901. M., 42. Beadle. History of bronchitis and influenza; fever, cough, bloody sputum, stridor; dulness over upper right. Cylindric-celled carcinoma of secondary bronchus in right upper lobe; metastases in right infra- and supraclavicular and axillary nodes.

76. WEINBERGER.[61] 1901. M., 52. Clerk. Pain in right chest, cough, dyspnea. Blood-tinged sputum with carcinomatous tissue; walnut-sized tumor of parietal bone; right main bronchus completely obstructed by carcinoma; metastases in liver, kidney, muscles, intestines, parietal bone and brain.

77. WERNER.[62] 1891. M., 65. Farm laborer. Bloody sputum for ten weeks; pain in right axilla, hip, left forearm; atypical epithelial cells in sputum; three lower spinous processes painful; tumor of bronchus to upper left lobe; glandular structure; metastases in left arm (fracture), lower vertebrae, neck of right femur.

78. WEST.[63] 1884. M., 39. Laborer. Dyspnea, emaciation, asthenia, night sweats; dulness over lower right. Carcinoma surrounding right main bronchus, reducing its lumen to one-third; secondaries in bronchial nodes and liver.

79. WOLF.[3] 1895. M., 60. Symptoms of cavitation. Cylindric celled carcinoma encircling and stenosing left chief bronchus 2 cm. below the bifurcation; bronchiectasis; metastases in liver and bronchial nodes.

80. WOLF.[3] 1895. M., 54. Musician. Anorexia, asthenia, emaciation; in left chief bronchus an ulcerating tumor obliterating its branches; left lung small and firm, right lung emphysematous. Cylindric-celled carcinoma; metastases in bronchial glands and peritoneum.

81. WOLF.[3] 1895. M., 47. Blacksmith. Pain in right side, dry cough, dyspnea; dulness and bronchial breathing on right; right chief bronchus entirely closed by tumor reaching 1.5 cm. above the tracheal bifurcation; bronchiectasis on right; left lung emphysematous. Carcinoma simplex; large polymorphous cells; secondaries in lungs, dura mater and liver.

82. WOLF.[3] 1895. M., 42. Factory-hand. Clinical picture was that of brain tumor; right chief bronchus partially closed and its mucosa ulcerated; tumor

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58. v. Schrütter: Ztschr. f. klin. Med., 1907, lxii, 508.

59. Wagner: München. med. Wchnschr., 1903, l, 133.

60. Watsuji, S.: Ztschr. f. Krebsforsch., Jena, 1903-4, i, 445.

61. Weinberger: Ztschr. f. Heilk., 1901, ii, 78.

62. Werner, M.: Das primäre Lungencarcinom, etc., Dissert., Freiburg, 1891.

63. West: Tr. London Path. Soc., 1884, xxxv, 87.

extends into both upper and lower lobes. Alveolar carcinoma with large polymorphous cells; metastases in spleen, kidneys and brain.

83. Wolf.[3] 1895. M., 58. Epistaxis, dyspnea, dulness over right apex; sputum became bloody; right main bronchus filled with cauliflower growth; left lung very emphysematous. Glandular celled carcinoma; secondaries in lungs, dura mater, nasal septum.

84. Wolf.[3] 1895. M., 55. Mechanic. Bilateral hydrothorax; wall of right main bronchus thickened; bronchiectasis on right. Carcinoma, alveolar in structure; large oval cells; metastases in liver, portal vein, retroperitoneal nodes and seventh and tenth thoracic vertebrae.

85. Wolf.[3] 1895. M., 56. Servant. Dyspnea, weakness, hemoptysis; dulness with bronchial breathing over entire left: left chief bronchus completely filled with tumor invading lower 3 cm. of trachea and constricting right bronchus; emphysema of right lung. Carcinoma, alveolar in structure; secondaries in thyroid and both adrenals. Origin from bronchial glands.

86. Wolf.[3] 1895. M., 67. Collector. Dyspnea, dysphagia, pain in left arm; flatness on percussion over upper left; death from suffocation; left chief bronchus occluded by growth from its own wall. Squamous-celled carcinoma; metastases in pericardium and retroperitoneal lymph-nodes.

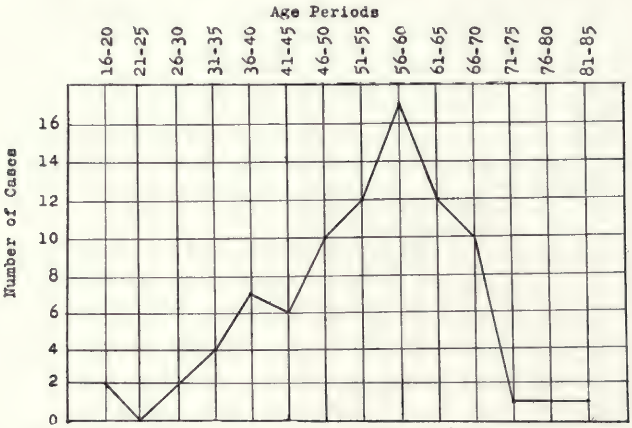

Fig. 5.—The age incidence of primary bronchial carcinomata by five year periods, based on a total of eighty-five cases. The abscissae indicate the number of cases, the ordinates the age periods.

87. Wolf.[3] 1895. M., 69. Mechanic. Clinical picture was that of phthisis; in right chief bronchus, 3 cm. below bifurcation, an oval ulcerated area; bronchiectasis on right. Squamous-celled carcinoma; metastases in bronchial lymph-nodes and liver.

88. Wolf.[3] 1895. M., 54. House porter. Abscess over eighth rib. Squamous-celled carcinoma blocking right main bronchus from bifurcation down, perforating superior vena cava and compressing right innominate; tuberculosis in pleura and right apex; secondaries in both kidneys and left adrenal.

89. Wolf.[3] 1895. M., 65. Mechanic. Clinical picture dominated by cerebral symptoms; tumor mass beneath eroded area in right chief bronchus; bronchiectasis. Squamous-celled carcinoma; metastases in right cerebral cortex and bronchial nodes.

The following case from the Medical Service of the University hospital also belongs in this group.

History.—Male, aged 47 (?), awning-maker. Brought to the hospital in an unconscious condition at 9:30 a. m., November 12, 1911. Only a brief history could be obtained from the patient's friends. He had not been as well as formerly for two years. Marked dyspnea for some time, with epistaxis and hemoptysis. The patient had believed that he had asthma, and stramonium leaves were found in his pockets. He became unconscious while seated in a chair in a hotel lobby.

Examination.—The following notes are taken from the hospital records: The patient was intensely cyanotic, skin dry, pupils evenly and markedly contracted, reacting but very little to light. There was marked dyspnea, with great activity of the accessory muscles. Respiration characterized by a short deep inspiration and long expiratory period. The rate was but 10 or 12 per minute. There were many râles during inspiration. No area of dulness was detected.

The heart was regular, apparently not enlarged, and the heart sounds were of good quality; the rate, 110. The radial pulse was of good size, quick, and fairly compressible.

The patient moved both arms readily but no spontaneous movements of the legs were noted.

The urine, obtained by catheterization, was negative except for a heavy trace of albumen. Tests for morphin applied to the urine were negative. Stomach washings contained only a little slimy mucus and a few fine particles of food.

The rectal temperature was 97.8 and 96 F.

Treatment.—A coffee and whiskey enema was retained. The stomach was washed with potassium permanganate solution, 1 to 500, and 1/150 gr. doses of atropin administered on the assumption that the case might be one of morphin poisoning. Oxygen was also used, and strychnin in 1/30 gr. doses.

Death occurred at 1:35 p. m. of the same day. Respiration ceased about one minute before the heart stopped beating.

Necropsy.—The autopsy was performed by Dr. A. S. Warthin at 9:00 a. m., Nov. 13, 1911. The more important points in the protocol dictated by Dr. Warthin are included below.

Thorax long; epigastric angle less than a right angle; superficial veins not dilated; a small amount of blood-stained mucus in the mouth.

Skull-cap very thin, otherwise negative; dura adherent all over the convexity; arachnoid slightly thickened; convolutions pale and edematous; section of brain otherwise negative.

No free fluid or gas in peritoneal cavity. Liver in median line two fingerbreadths below the ensiform. The diaphragm rises to the level of the fifth rib on the right and the sixth rib on the left.

No free gas or fluid in the thoracic cavity. There are a few small adhesions between the visceral and parietal pleurae, most marked at the right apex where the pleura shows a dense hyaline thickening; no enlarged lymph-nodes in the anterior mediastinum.

Apex of the heart at the sixth interspace in nipple line. Auricles, particularly the right, distended with unclotted blood. Mitral orifice somewhat larger than normal, admitting two fingers with ease; tricuspid admits four fingers; valve flaps negative.

Orifices and valve flaps of pulmonary artery and aorta negative. No narrowing of lumen of aorta and no aneurysm.

Left lung: Anterior border extends to left sternal line. Large bronchi filled with creamy exudate; bronchial nodes small and heavily pigmented; moderately voluminous; marked congestion and edema.

Right lung: Anterior border extends to right sternal line. The lung is bound by many adhesions to a tumor the size of an orange which is connected with the bronchial nodes, the esophagus and the descending aorta. The tumor mass completely surrounds the main bronchus to the right lung and has infiltrated and destroyed the bronchial wall. The lumen of the bronchus is markedly narrowed (Fig. 1). The tumor also extends along the bronchus to the upper lobe.

At the level of the bifurcation the trachea is much stenosed by the pressure of the tumor mass. This stenosis affects the left main bronchus more than the right. The former barely admits a glass rod 2 mm. in diameter. The lumen of the esophagus is also narrowed at the same level and the wall is firmly attached to the tumor mass.

Spleen: Small; capsule slightly wrinkled and contains numerous small hyaline thickenings; atrophy of pulp and follicles, increase of stroma.

Left kidney: Fibrous capsule strips easily. On section the parenchyma is deep purplish red, bleeds freely. Several small grayish nodules beneath the surface.

Right Kidney: Shows less passive congestion than the left, otherwise similar.

Adrenals: Normal in size: medulla preserved.

Large and Small Intestines: Partially distended with gas; duodenum negative; pylorus patent; stomach mucosa slightly atrophic; no erosions or hemorrhages.

Pancreas: Congested and softer than normal.

Liver: Capsule somewhat thickened and contains small hyaline areas; parenchyma shows a marked acute passive congestion; gall-bladder shows old adhesions.

Abdominal aorta shows patches of sclerosis and atheroma.

Retroperitoneal lymph-nodes are atrophic and congested.

Microscopical Findings.—The most important microscopical findings follow:

Heart: Atrophy; fatty degeneration; arteriosclerosis of coronaries.

Spleen: Atrophy; chronic passive congestion; acute congestion; hyaline thickening of capsule.

Brain: Congestion, edema, chronic leptomeningitis.

Kidneys: Acute passive congestion, atrophy, cloudy swelling, metastatic adenocarcinoma.

Right Lung: Chronic abscess, chronic fibroid pneumonia, bronchiectasis, chronic passive congestion.

Left Lung: Emphysema, chronic passive congestion.

Liver: Atrophy, chronic passive congestion, hyaline areas in capsule are thickenings with hyaline blood-vessels, probably nearly healed angiocavernosa.

Pancreas: Atrophy, sclerosis, post mortem change.

Neoplasm: After formaldehyd fixation and paraffin infiltration, sections of the neoplastic tissues were stained in hematoxylin and eosin, carbol-kresyl-echt-violett, Bismarck brown and hematoxylin and picric acid. The primary tumor mass shows an adenocarcinoma with irregular gland-like spaces (Fig. 2) which are lined by two or more rows of epithelial cells, with large spherical or oval nuclei. There is some tendency for the oval nuclei to be arranged with their long axes parallel to each other and perpendicular to the lumina, giving a marked cylindric-celled appearance. The cell nuclei stain readily but not intensely with the various basic stains. The alveolar spaces are filled with a finely granular material which takes a bluish stain with hematoxylin and reacts metachromatically with carbol-kresyl-echt-violett, thus resembling mucin in every particular.

The same architectural and cell characteristics are found in all parts of the neoplasm examined. In the more peripheral portions of the growth such as the part invading the esophageal wall (Fig. 3) the alveolar spaces are smaller.

Even in the metastases in the kidney (Fig. 4) mucin formation has taken place.

The neoplasm must be considered a primary adenocarcinoma of the right main bronchus, cylindric-celled in character, probably arising from the bronchial mucous glands.

GENERAL CONSIDERATIONS

Frequency.—The number of cases reported indicates that bronchial carcinoma is not as rare a disease as has been supposed. Wolf[3] found lung and bronchial carcinomata in .223 per cent. of 20,116 autopsies and Pässler considers 87 per cent. of the neoplasms in this group to be of bronchial origin. The difficulty in diagnosing the condition has done much to keep down the percentage, but now that its frequency of occurrence is more fully realized and search is being made for it, the ratio of incidence is being raised. This is shown by the statistics of the combined lung and bronchial group which Adler[1] presents in his monograph. A summation of the more recent statistics gives forty cases in a total of 11,093 autopsies, that is, .36 per cent.

Age.—The age was given in eighty-five of the eighty-nine cases in our own list. The distribution over five-year periods is shown by Figure 5. The maximum number is found in the age period 56 to 60, inclusive, but the possibility of occurrence in very young individuals is emphasized by the cases of Hall and Tribe[22] and of Horn,[29] in which the patients were 17 and 18, respectively.

Sex.—In eighty-seven cases, seventy patients were males and seventeen females. Pässler found the ratio to be fifty males to eighteen females in his list of both lung and bronchial carcinomata. After making due allowance for the usual preponderance of male patients in the hospitals from which many of the cases are derived, it still seems evident that bronchial carcinoma is much more common in males than in females.

Location.—Much stress has been laid on a supposed excess of cases of carcinoma of the right bronchial tree as compared to the left. Reinhard,[64] for instance, reported eighteen lung carcinomata from the right side and nine from the left. This disproportion has been attributed to the larger size and more direct course of the right main bronchus with the thought that it would be subjected to a greater degree of mechanical irritation than the left. Adler,[1] in his combined lung and bronchial list, finds the right side more frequently affected than the left, but thinks that the difference is too small to serve as a basis for a theory. We find the two sides to be involved with approximately equal frequency.

Left side	28 cases
Right side	27 cases
Both sides	14 cases

Etiology.—The data in regard to occupation are too meager to permit the drawing of definite conclusions. The case of Boyd,[9] in a bottle-blower, those of Beck,[7] Georgi,[19] and Wolf[3] in blacksmiths, with Handford's[24] in a collier, may be picked from the twenty-five of known occupation as instances in which opportunity for chronic bronchial irritation is obvious. In discussing the etiology of this group, Wolf[3] mentions luetic scars and ulcerations, but puts the most emphasis on a breaking through of softened pigmented lymph-nodes into the bronchial lumen. He says that the *"Pigmentdurchbrüche"* occur especially in the chief bronchi just below the bifurcation and more often on the right side than on the left. This theory has not been supported by the microscopical

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64. Reinhard, W.: Arch. d. Heilk., 1878, xix, 369.

findings in subsequent cases, and the part played by dust inhalation requires further study. A very suggestive fact is the preponderance of cases in males who, through occupation and the use of tobacco, are more exposed to the inhalation of irritating substances than are females (Adler[1]).

In but three cases was the disease attributed to trauma. Two of these were from falling (Hinterstoissen[27] and Handford[24]), and the other from a blow on the chest from a piece of iron (Georgi[19]). We may, therefore, be certain that gross trauma is not an important etiological factor.

In a very few instances squamous-celled carcinomata have been described as developing in the walls of bronchiectatic or tuberculous cavities (Kaufmann[67]). The series of cases here reviewed indicates, however, that bronchiectasis is a result rather than a cause of the neoplastic growth. Bronchiectasis is specifically mentioned in fifteen of the case reports, but it occurs in the peripheral portions of the lung rather than at the site of the tumor, and is usually accompanied by atelectasis. It must be considered as due to the stenosis of the bronchus and the inflammatory changes in the lung parenchyma.

In eleven cases out of the eighty-nine a coincident tuberculosis is mentioned. This is usually apical and in two or three instances is spoken of as "old" or "healed." There is nothing to indicate that the tuberculosis was in any way a direct causal factor. It would rather seem that some chronic inflammatory process in the lungs such as tuberculosis, chronic bronchitis or chronic pneumonia, which is also rather frequently found in these histories, may be indirectly the inciting influence. More complete histories of the previous condition of the patient must be had before the importance of these factors can be fully established.

Point of Origin.—Primary carcinoma of the bronchi may arise either from the bronchial mucosa or from the epithelium of the bronchial mucous glands. Analysis of the cases listed gives the following results:

Origin from mucous glands	22
Origin from bronchial mucosa	17
Uncertain or unspecified	50

Of the adenocarcinomata, eighteen are referred to a glandular origin and six to the mucosa. All of the squamous-celled type, in which the point of origin is given, are said to have arisen from the mucosa. In the latter case, there is much in favor of the theory that the malignant change is associated with a metaplasia of the surface epithelium to the squamous type. The case of Davis and Le Count is illustrative, for the mucosa was found to resemble skin from a centimeter above the tracheal bifurcation to a point some distance along each of the main bronchi.

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67. Kaufmann: Lehrbuch der Speziellen Pathologischen Anatomie, p. 303.

Von Schrötter[58] also argues for a metaplastic origin for the squamous-celled type rather than referring it to an embryonal anlage.

In the case here reported the origin was probably from the mucous glands. As in many other neoplasms of similar character, the *"Uebergangsbilder,"* which would prove this point, are lacking. However, many sections taken along the main bronchus show small islands of tumor, occupying the normal position of mucous glands, equaling normal mucous glands in size, and themselves containing mucus. At this same point the bronchial mucosa is inflamed and eroded, but nowhere neoplastic. The general architecture of the tumor is also very suggestive of the glandular origin.

Histopathology.—In fifty-five cases, the general structural character of the neoplasm is given. It is spoken of as

Alveolar, ascinar or adenomatous	in 45 cases
Medullary	in 5 cases
Scirrhous	in 3 cases
Simplex	in 2 cases

This shows an unduly large number of the first group, for in most of the cases described as "squamous," nothing is said in regard to structure. According to cell type, we find these carcinomata described as

Squamous celled in	25 cases
Cylindric celled in	18 cases
Polymorphous celled in	10 cases
Round or oval celled in	2 cases
Gland celled in	1 case
Cuboidal celled in	1 case

It is probable that most of the cases in the last four groups might have been placed in one or the other of the first two. The two chief forms of bronchial carcinomata are, therefore, the adenomatous cylindric-celled type and the squamous-celled type.

As has been described, mucus formation was a prominent feature in the histological picture of our own case. It is mentioned in ten of those listed, all adenomatous in character. The extent of mucus production varies from the formation of intracellular vacuoles, as in the case of Beck,[7] to the filling of large alveoli with metachromatically staining mucin, as in the cases of Stropeni[56] and Dömeny.[12] Boecker[8] and Horn[29] consider that mucus formation does not prove an origin from the bronchial mucous glands, although in most of the other cases such an origin is maintained. Mucus formation in the metastases has been noted in three cases, including our own.

Metastases.—The proneness of lung and bronchial carcinomata to give rise to metastases has been much emphasized. Wolf[3] found secondaries in twenty-one cases out of twenty-three; Pässler,[5] in sixty-three cases out of seventy-four. The figures from our list of exclusively bronchial carcinomata closely parallel these.

Metastases found to be present	70 cases
Metastases not mentioned	11 cases
Metastases not found	9 cases

The locations of the secondary growths were the most varied. Some unusual sites are mentioned, such as in the finger (Hinterstoissen[27]), and nasal septum (Wolf[3]). It is unnecessary to give a complete enumeration of the secondaries found, but the bronchial, cervical and axillary lymph-nodes, liver, kidneys and adrenals were most frequently involved. In the case here reported, the only secondaries were those found in the kidney. Two other observations should be mentioned.

1. The proneness to brain metastases, which are found in twelve cases. The clinical picture may be dominated by such secondaries. Dömeny[12] reports a case in which the chief findings were pain in the head, visual and auditory disturbances and choked disk. In this instance there were seven brain metastases from a bronchial adenocarcinoma.

2. The frequent occurrence of palpable secondaries in the lymph-nodes. In thirteen cases such nodes were noted, usually cervical, supraclavicular or axillary. The reported cases show that, as a rule, if the glands of but one side are invaded the neoplasm will be found to involve the bronchus of the same side.

SYMPTOMATOLOGY AND DIAGNOSIS

In a few cases an ante mortem diagnosis of bronchial carcinoma is absolutely impossible. Such cases fall into three groups: (1) those in which the neoplasm is very small and is discovered only incidentally, as in the case reported by Klüber;[33] (2) those in which the clinical picture is dominated by cerebral or other metastases, as in one of Wolf's cases; (3) those in which the patients are practically moribund when first seen. The case here reported falls in the last group.

On the other hand, diagnosis is often possible, as is shown by the fact that in about ten of the cases listed in this paper the nature of the process was ascertained before necropsy. With the additional aids now available the proportion of diagnosed cases should be very much increased.

The chief symptoms mentioned in the clinical histories of the listed cases, in the order of their frequency, are as follows:

1. *Cough.*—Sometimes this is spoken of as a "dry" cough, but the case reports give no characteristic description.

2. *Dyspnea.*—This very frequent symptom is usually progressive in character, becoming more and more severe, and oftentimes terminating in the death of the patient in a suffocative attack.

3. *Hemoptysis.*—Hemorrhage, ranging from a bloody streak in an otherwise mucopurulent sputum to a brisk flow of bright red blood, is one of the most common findings. In forty-two cases in which the character of the sputum is mentioned, there was some degree of hemoptysis in thirty-five. The "black-currant jelly" or "raspberry jelly" sputum once thought to be characteristic of lung and bronchial carcinomata is rarely mentioned in case reports.

4. *Pain.*—Pain is also frequently a factor in the clinical picture. It is felt in the chest, usually on the affected side, or in that shoulder and arm. Here it may be explained as a referred pain, or it may be due to pressure on the brachial plexus from a secondary involvement of axillary or clavicular nodes.

5. *Pressure Symptoms.*—The group of symptoms arising from pressure of the neoplasm on surrounding structures is of great diagnostic value. From obstruction to the venous return we have dilatation of the superficial veins of head and thorax, often accompanied by edema. These changes are mentioned in nine cases. In five paralysis of the recurrent laryngeal is noted and two others showed aphonia. Dysphagia is reported in four instances, and in one pupillary inequality and ptosis of one lid developed.

The usual absence of fever and night sweats from the symptom complex is worthy of note. In but four of the ninety cases is fever mentioned.

The physical findings vary with the extent of the neoplasm, with the degree of stenosis of the bronchi and with complicating lung conditions. The usual percussion findings are dulness in the lobe or lobes supplied by the affected bronchus and hyperresonance in the opposite lung. The dulness depends largely on atelectasis due to air absorption from the alveoli of the lobes of which the bronchi have been blocked. The hyperresonance is due to a compensatory emphysema in the opposite lung. Signs of cavitation in the affected lung are also frequently found. In the bronchial type of pulmonary carcinoma cavity formation is usually due to bronchiectasis rather than to breaking down of the neoplasm, a process to which it is often erroneously referred. As previously mentioned, bronchiectasis is practically always found in the portion of the bronchial tree beyond the stenosis. In general, it may be said that the physical findings in bronchial carcinoma are those of bronchial obstruction.

Bronchoscopic examination may confirm a diagnosis of bronchial carcinoma. Rénon, Géraudel and Marre[65] report such a case (not included in list through lack of autopsy findings), in which the lower portion of the left main bronchus was seen to be entirely obstructed by a neoplastic growth. A piece of the tumor was removed through the bronchoscope, examined microscopically, and found to be squamous-celled in character.

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65. Rénon, L.: Géraudel et Marre. Presse méd., Paris, 1910, xviii, 401.

Radioscopy is of the greatest service in these cases. After describing thirteen cases of lung and bronchial carcinoma which were examined radioscopically, Otten[66] concludes that tumors arising from a large bronchus at the hilus and spreading into the lung as a compact mass, should give little difficulty; that differentiation is difficult when the neoplasm spreads diffusely along the bronchial tree, and that the skiagram gives the most certain information of any method in regard to the precise localization, the manner of spreading and the extent of bronchial neoplasms.

No opportunity should be lost to obtain evidence in regard to the histological character of the neoplasm. This may often be accomplished by the excision of a metastatic growth, as previously mentioned; by removal of a specimen through the bronchoscope, or by careful search of the sputum. The atypical cells were recognized in the sputum in four of the cases in our list. Stropeni[56] said that no symptom was pathognostic except the finding of tumor cells in the sputum, but now bronchoscopic examination and removal of a specimen may be added as an even more satisfactory procedure.

Treatment.—In the past the diagnosis of bronchial carcinoma has been considered as chiefly of prognostic value. However, in the rapid advance in intrathoracic surgery the condition is becoming an operable one. Ders[68] reports a total resection of a carcinomatous lung, in which case the death of the patient resulted from a septic process developing in the lung stump. In Lenhartz'[69] group of cases a resection of a carcinomatous lobe is reported in which the patient remained comparatively well one and a half years after the operation. Küttner[70] and Sauerbruch[70] have also removed large sections of carcinomatous lungs with success. The early diagnosis of this condition therefore becomes a matter of the greatest importance, for only through an early diagnosis can the patient be offered any hope of relief or cure. With this in view, bronchial carcinoma should always be considered a possibility in diagnosing lung conditions. Patients with cough, dyspnea, hemoptysis or pressure symptoms in various combinations of intensity should be studied by the newer diagnostic methods which have been applied to this condition. In doubtful cases, Adler[1] advises an exploratory thoracotomy.

Modern lung surgery furnishes the greatest incentive for the early diagnosis of bronchial carcinoma, and it is hoped that this study will aid in making such diagnoses possible.

I wish to acknowledge my gratitude to Dr. A. S. Warthin for his supervision and assistance in the preparation of this study.

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[66] Otten, M.: Fortschr. a. d. Geb. d. Röntgenstrahlen, Hamburg, 1906, ix, 369.

[68] Ders: Centralbl. f. Chir., 1911, xxxviii, 427.

[69] Lenhartz: Cited by Brauer, Centralbl. f. Chir., 1911, xxxviii, 427.

[70] Küttner, Sauerbruch: Cited by Batzdorff. Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1912, xxi, p. 1.

The Relation of Fatigue to Paralysis Localization in Plumbism

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Reprinted from the Archives of Internal Medicine
October, 1913, Vol. 12, pp. 399-419

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CHICAGO
American Medical Association
Five Hundred and Thirty-Five Dearborn Avenue
1913

THE RELATION OF FATIGUE TO PARALYSIS LOCALIZATION IN PLUMBISM *

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The apparent predilection of lead and its salts for the extensor muscles of the wrist, or the musculospiral nerve which supplies them, has for a long time remained unexplained.

This peculiar localization, as well as changes in the muscles themselves, has formed subject matter for numerous hypotheses. One of the oldest views, which is now almost obsolete, held that the paralysis was due to intramuscular changes. The spinal view was held by Remak and Erb, but the preponderance of opinion at present points to the peripheral nerves as the most likely origin, and even Remak himself admits the lack of convincing testimony in favor of the spinal origin. "The constancy of peripheral changes and the infrequency of noteworthy changes in the cord make the peripheral the more probable theory; but if it is correct, there is yet no explanation of the almost regular escape of certain muscles from the paralysis."[1]

With the hope of elucidating this interesting point, Dr. Warthin suggested that I make an attempt to corroborate the view which is known as Edinger's theory. He explains these peculiar saturnine paralyses as the result of excessive strain on certain groups of muscles. In this way, he accounts for the common wrist drop.

His conclusions are as follows:

(a) Of the forearm, the flexors (triceps, anconeus, extensors, biceps, brachialis anticus and supinator longus) possess a high degree of capacity for work; while the supinators are characterized by great mass, and are brought into play mainly in work of coarse and heavy nature, and not during fine manipulation.

(b) The muscles concerned in pronation are of small capacity for work, and are not called on for sustained work. As for the muscles acting on the wrist and hand, he concludes that the extensors (carpi radialis longior and brevior, carpi ulnaris and the extensors of the fingers) are powerful, and much exceed in capacity for work the flexors (flexor carpi radialis, flexor carpi ulnaris, the flexors of the fingers, etc.), but in all fine manual work, and especially where close grasping move-

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* Submitted for publication July 10, 1913.

* From the Pathological Laboratory, University of Michigan.

[1] Edsall: Osler's Modern Medicine, i, 96.

ments enter into association with the flexors, external strain is put on them, while the flexors merely support their action. The extensor communis digitorum is the weakest of all the long finger muscles; its volume is hardly one-fourth that of the corresponding flexor, and while it acts only on the first of the phalanges, the flexors act on all three. In all fine work they are called on for heavy strain, especially the interossei and the lumbricales, but in harmony with the long flexors when grasping movements are performed. The small muscles of the fingers have nearly the same mass as the extensor communis, and in all fine movements or grasping efforts are taxed severely; but their play is under considerably more favorable physical relations than that of the extensors, while at times they are aided by the long flexors. The chief adductor muscle of the thumb (extensor metacarpi pollicis) is particularly powerful; the other extensors of the thumb are very weak and work under unfavorable physical conditions, but are supported in their action by the strong adductor muscle. The muscles of the abductor opponens and flexor brevis in the complicated work thrown on the thumb in manipulation are much exerted, so that the effects of over-exertion show themselves first in this region.

Thus Edinger maintains that the muscle-supply of the arm is designed for heavy work, the muscles of the finger and hand having to carry more work than can be expected of them from a consideration of their volume and physical action.

Teleky[2] reviews forty cases of paralysis with special reference to this theory. Thirteen were cases of the antibrachial type of D'jerine-Klumpke. In only one was the left hand affected, while in all the others except one, the right hand was affected. In it both hands suffered. These facts are significant in their relation to causation by employment.

The paralysis of the small muscles of the hand is rather characteristic in file cutters. As is known, these muscles are used predominately in this trade. Goadby and Legg[3] have frequently observed the decrease in size of the thumb and hypothenar eminences in lead rollers.

Of fourteen painters suffering from plumbism, Teleky[2] found three with paralysis of the right forearm only, while the remainder had both arms affected, but always more marked in the right than in the left. In some of these, the shoulder muscles were paralyzed, owing to the strain caused by raising the arms above the head, or lying on the back to paint the running gears of carriages.

Particularly interesting are the cases cited by Teleky in lead capsule polishers. These cases showed right-sided paralysis of the adductor brevis pollicis supplied by the median nerve, and partial paralysis of the

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2. Teleky: Deutsch. Ztschr. f. Nervenheilk, 1909, xxxvii.
3. Goadby and Legg: Lead Poisoning and Lead Absorption, Longmans & Co.

long extensors and of the extensor ossis metacarpi pollicis supplied by the radial nerve, and in one or two cases complete paralysis of the thenar muscles, and adductor, while the extensors of the fingers and wrists were only partially paralyzed. This unusual muscular involvement is undoubtedly the result of the peculiar movement necessary in polishing the capsules of bottles on a revolving spindle, involving especially the use of the opponens muscle.

Teleky reports a shoemaker who was poisoned with white lead. He developed not only paralysis of the adductors and extensors of the thumb, but also a paralysis of a lower extremity. He explains the latter by the exertion thrown on the adductor muscles of the thigh while holding the shoe.

In children affected with lead palsy the frequency of paraplegia has often been noticed. Both Oliver[4] and Goadby and Legg,[3] as well as Escherich and Variot[5] make mention of it.

I have to report as an original clinical observation, a painter, who, when plying his trade, had more climbing of ladders and mixing of paints to do than actual work with the brush. He developed muscular weakness and paraplegia some time before developing the wrist drop.

Goadby and Legg[3] have poisoned cats experimentally, and found that the quadriceps extensor muscles supplied by the anterior crural nerve was the first group affected, while soon after the lumbar group of spinal muscles was involved. This selection is significant, considering that these are the groups used in jumping movements.

These observers have also found hemorrhages in the nerve (anterior crural) and consider the minute hemorrhages resultant on the degeneration of the venioles to be of paramount importance in the pathology of lead poisoning.

From these observations from varied sources, one fact stands out rather strikingly — there is no necessary anatomical relationship of the paralysis in plumbism, but the functional relationship of involved muscles seems essential.

Gombault[6] sought to explain the paralysis of the hand and arm muscles by the absorption of lead through the skin, but this hypothesis is rather absurd when we come to account for the ocular or shoulder paralysis, or even that of the lower extremities.

Quoting from Alice Hamilton's article,[7] Labbe is authority for the statement that storage battery workers suffer from paralysis of the shoulder muscles. Bernhardt and Leichtentritt speak of the paralysis of the left fingers and thumb in file makers who grasp the chisel with the left hand.

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[4] Oliver: "Occupational Pathology."

[5] Escherich and Variot: Jour. Am. Med. Assn., 1911, lvi, 1240. Quoted in Alice Hamilton's Article.

[6] Gombault: Arch. Physiol., 1873.

[7] Hamilton, Alice: Jour. Am. Med. Assn., 1911, lxi, 1240.

Patch[8] relates a case of marked atrophy and paralysis of the shoulder muscles in a man who ran a "delicatessen." He was accustomed to do much lifting and first noticed that he was not able to lift as much as formerly. He presumably contracted the disease by substitution of a lead pipe in the connections of his soda fountain. C. H. Snover[9] of Randolph, N. Y., reports a case of a 16-year-old girl who sealed cans in a milk condensery. He says in part:

> With arms extended, there was a marked wrist drop, especially on the right. The patient used the right hand to use the soldering iron. The left hand could be extended to bring it in line with the forearm, but no more, and this only with difficulty. No extension was possible in the right hand.

A. DETERMINING THE SUSCEPTIBILITY OF THE FROG TO NEUTRAL LEAD ACETATE. (FROGS 1 AND 2)

	Date	Amount of Lead Given	Notes
Frog 1...... Wt. 30 gm.	11/15/12	One c.c. sat. aqueous neutral lead acetate into dorsal lymph-sac.	11:30 a. m. Moderate stupor and diminution of reflexes.
	11 a. m.	All structures in right thigh ligated except the sciatic nerve. Frog pithed. Reflex irritability soon recovered.	12:00 m. Increase of stupor. Crossed reflexes negative. 1 p. m. Reflexes disappeared. 1:30 p. m. Death, as determined by cessation of circulation in the web of the foot. Reaction to weak induction shock. Stimulation of the right and left gastrocnemii, both directly, and by way of the sciatic nerve is positive.
Frog 2...... Wt. 27 gm.	11/15/12	Two c.c. neutral lead acetate into dorsal lymph-sac.	2:15, stupor and reflex diminution.
	2 p. m.	Same as above.	2:30 marked stupor. Cross reflexes negative. 3:00, increase of stupor. 3:45, death. Reaction to weak induction shock same as above.

Since the fatigue basis has such logical clinical verification, Dr. Warthin thought it wise to ascertain what could be accomplished experimentally to validate this claim.

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[8] Patch: Boston Med. and Surg. Jour., 1909, 653.

[9] Snover, C. H.: Jour. Am. Med. Assn., 1911, lvi, 1799; case report.

In these experiments, frogs were the animals selected, because they were most convenient for stimulation and because the results of fatigue could be accurately computed in a mechanical way. It was first necessary to determine their susceptibility to a soluble salt of lead, and also interesting to determine its sphere of action. To this end the Curare Experiment was performed with lead acetate. Briefly, this consists in ligation of all the structures of the thigh, excepting the sciatic nerve, and then the injection of the poison into the dorsal lymph-sac.

B. DETERMINING THE MINIMUM LETHAL DOSE OF NEUTRAL LEAD ACETATE IN FROGS. FROGS THREE TO EIGHT, INCLUSIVE.

SERIES ONE

	Date	Amt. of Lead Into Dorsal Lymph-Sac c.c.	Results
Frog 3 ..... Wt. 28 gm.	11/17/12 8 a. m.	0.25	Negative at any time.
Frog 4	11/17/12 8 a. m.	0.50	9 a. m., stupor and diminution of reflex, which gradually abated and frog finally recovered.
Frog 5 ..... Wt. 30 gm.	11/17/12 8 a. m.	0.75	9 a. m., stupor and reflex diminution. 10 a. m., stupor marked. Condition grew progressively worse until 3 p. m., when frog died.

SERIES TWO

Frog 6 ..... Wt. 27 gm.	11/18/12 8 a. m.	0.5	Same as 4
Frog 7 ..... Wt. 29 gm.	11/18/12 8 a. m.	0.6	11 a. m., slight stupor. 12 m., increase. 6 p. m., dead
Frog 8 ..... Wt. 30 gm.	11/18/12 8 a. m.	0.7	10 a.m., slight stupor. 11 a.m., marked stupor. 3 p. m., dead.

0.6 c.c. saturated aqueous solution neutral lead acetate is M. L. D. for 30 gm. frog; or 0.02 c.c. per gm.

Two c.c. saturated solution of lead acetate were so injected into a 25-gm. frog, which killed it in about two hours. The animal failed to respond to reflex stimulation, this failure being of gradual development. Direct application of the electrodes to the muscles provoked a marked response. Stimulation of the sciatic nerves also produced marked muscular contraction. At no time were any crossed reflexes observed. This experiment proves that the frog is susceptible to lead acetate, and that it does

C. DETERMINING THE RESULTS OF FATIGUE PRODUCED BY THE DIRECT METHOD IN LEAD POISONED FROGS. FROG 9. WEIGHED 25 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12 /2/12 5 p. m.	0.5	15″	10½	Stimulation applied to right gastrocnemius muscle; an electrode at either end.
12/ 3/12	...	15″	10½	Frog shows stupor.
12/ 4/12	...	...	....	Reacts poorly.
12/ 4/12	...	14″	10½	Stupor. Reacts poorly.
12/ 6/12	...	...	....	Frog normal again.
12/ 7/12	...	15″	10½	Induration at electrodal points.
12/ 8/12	...	13″	10½	
12/ 9/12	...	13″	10½	Stupor.
12/10/12	...	...	....	Frog dead.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right negative to weak current; positive to strong current.

Left at 10½ negative; 9 cm. positive.

Sciatics: Positive at 10½. Right gastrocnemius shows 97.3 gm. millimeters of work; left, 112.4 gm. millimeters of work.

FROG 10. CONTROL TO FROGS 9 TO 20. WEIGHT 28 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 2/12	...	15″	10½	Stimulation applied to right gastrocnemius an electrode at either end.
12/ 3/12	...	15″	10½	
12/ 4/12	...	15″	10½	
12/ 6/12	...	Rest	....	
12/ 7/12	...	13″	10½	Induration at electrodal points.
12/ 8/12	...	12″	10½	
12/ 9/12	...	14″	10½	
12/10/12	...	...	....	Frog killed.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right at 10½ cm. weak; at 9 cm. strong.

Left at 12 cm. strong.

Right gastrocnemius, 132.6 gm. millimeters of work; left, 252.4 gm. millimeters.

not perceptibly affect the muscles directly, the end plates or the peripheral nerves. Since the animal's brain was destroyed by pithing, by exclusion we arrive at the fact that in the frog the spinal cord is the sphere of action of lead, given in doses sufficient to produce acute effects. (See Section A, Frogs 1 and 2, Protocol of Experiments.)

FROG 11. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 4/12	0.35	12″	10	Direct Stimulation of right gastrocnemius.
12/ 5/12	...	13″	10	
12/ 6/12	...	12″	10	Moderate stupor.
12/ 7/12	...	12″	10	Moderate stupor.
12/ 8/12	...	12″	10	
12/ 9/12	...	12″	10	
12/10/12	...	...	....	Killed frog.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right, 10 negative and 9½ negative; 8 cm. positive.

Left, 10 cm. negative; 9 cm. positive.

Sciatics: Positive at 10½ cm. Right gastrocnemius, 107 gm. millimeters of work; left, 117.5 gm. mil. of work.

FROG 12. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 6/12	0.3	12″	10	Direct stimulation of right gastrocnemius.
12/ 7/12	...	12″	10	
12/ 8/12	...	12″	10	
12/ 9/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	Killed frog.

Reaction to Induction Shock:

Practically the same as in No. 11.

Work: Right gastrocnemius, 104.3 gm. mil.; left, 119.1 gm. mil.

A saturated aqueous solution of neutral lead acetate was used exclusively in all the experiments, because it is the most soluble salt. It was always injected into the dorsal lymph-sac. The weight of the frogs was always between 25 and 35 gm.

It was next necessary to determine the minimum lethal dose of lead acetate for these animals. (See Protocol of Experiments, Section B, Frogs 3 to 8, inclusive.) In Series I of three frogs, Frog 3 was given 0.25 c.c. of the lead solution, and the dose progressively increased by an increment of 0.25 c.c. in the remaining two. The first two frogs of the

FROG 13. WEIGHT 25 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	13″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	13″	10	
12/11/12	...	13″	10	
12/12/12	...	13″	10	
12/13/12	...	13″	10	
12/14/12	...	13″	10	
12/15/12	...	13″	10	
12/16/12	...	13″	10	
12/17/12	0.3	13″	10	
12/22/12	...	...	10	Frog killed.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right, 11 cm. negative; 10 cm. negative; 9½ cm. positive.

Left, 11 cm. negative; 10 cm. positive.

Work: Right, 119.2 gm. mil; left, 173.8 gm. mil.

FROG 14. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	No symptoms.
12/14/12	...	12″	10	No symptoms.
12/15/12	...	12″	10	No symptoms.
12/16/12	...	12″	10	No symptoms.
12/17/12	0.35	12″	10	
12/22/12	...	...	....	Killed frog.

Reaction to Induction Shock:

Gastrocnemii, direct application:

Right at 9 cm. positive; at 10 cm. negative.

Left at 11 cm. positive

Work: Gastrocnemius, right, 125.2 gm. mil.; left, 169.7 gm. mil.

FROG 15. WEIGHT 32 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	Frog died; no result.

FROG 16. WEIGHT 27 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.4	12″	10	No symptoms.
12/22/12	...	...	....	Killed frog.

Reaction to Induction Shock:
  Gastrocnemii, direct application:
    Right at 9 cm. positive; at 10 cm. negative.
    Left at 12 cm. positive.
  Work: Right gastrocnemius, 127; left, 178.4.

FROG 17. WEIGHT 28 GM.

Date	Amount of Lead, c.c.	Stimulation Amount of	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.45	12″	10	
12/18/12	...	12″	10	Slight stupor.
12/19/12	...	12″	10	Recovered.
12/22/12	...	...	....	Frog killed.

Reaction to induction shock and work practically the same as in Frog 16.

series (Frogs 3 and 4) recovered from doses of 0.25 c.c. and 0.5 c.c. of lead, respectively. Number 5 died with a dose of 0.75 c.c. The frogs in Series II (Frogs 6, 7 and 8) received, respectively, 0.5, 0.6 and 0.7 c.c. of lead. Number 6 recovered and Nos. 7 and 8 died from the effects of the lead. Thus 0.6 c.c. is the M.L.D. of neutral lead acetate for a 30-gm. frog, or 0.02 c.c. per gram.

FROG 18. WEIGHT 33 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.48	12″	10	
12/18/12	...	12″	10	Progressive stupor.
12/19/12	...	12″	10	Progressive stupor.
12/20/12	...	12″	10	Progressive stupor.
12/21/12	...	...	10	Frog killed.

Reaction work practically the same as in Frog 16.

FROG 19. WEIGHT 31 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of right gastrocnemius.
12/10/12	...	12″	10	
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.5	12″	10	
12/18/12	...	12″	10	Progressive stupor.
12/19/12	...	...	....	Frog killed.

Reaction to even strong induction slight, and work practically *nil.*

In Section C of Experiment Protocol, it is seen that 12 frogs were used. With these the direct method of stimulation prevailed throughout. This method consisted in the direct application of the electrodes at either end of the gastrocnemius muscle. To obtain a suitable place for the electrodes, the muscle was denuded over an area of approximately 6 mm. square. This method was open to the objection that after varying lengths of time, the muscle underwent changes deleterious to the success of the experiments, as it afterward proved. Petechiae, induration and occasional sloughing occurred at the electrodal points. It is self-evident that the more serious change would disqualify the muscle, and presumably the slighter changes were without favorable influence.

FROG 20. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
12/ 9/12	...	12″	10	Direct stimulation of
12/10/12	...	12″	10	right gastrocnemius.
12/11/12	...	12″	10	
12/12/12	...	12″	10	
12/13/12	...	12″	10	
12/14/12	...	12″	10	
12/15/12	...	12″	10	
12/16/12	...	12″	10	
12/17/12	0.5	12″	10	
12/18/12	...	12″	10	Marked stupor.
12/19/12	...	...	....	Frog killed.

Reaction to induction shock negative, even to strong current. Work practically *nil.*

D. DETERMINING THE RESULTS OF FATIGUE BY THE INDIRECT METHOD IN LEAD POISONED FROGS

FROG 21. WEIGHT 28 CM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
1/ 5/13	...	12″	8–9	Left gastrocnemius
1/ 6/13	...	12″	8–9	fatigued by indirect
1/ 7/13	...	12″	8–9	method. No symp-
1/ 8/13	...	12″	8–9	toms at any time.
1/ 9/13	...	12″	8–9	
1/10/13	...	12″	8–9	
1/11/13	...	12″	8–9	
1/12/13	...	12″	8–9	
1/13/13	0.125	12″	8–9	
1/17/13	...	...	...	Frog killed.

Reaction to Induction Shock:
All muscles react well at 12 cm.
Work: Right gastrocnemius, 265.4 gm. mil.; left, 27.8 gm. mil.

Recourse to Section C shows considerable variance in the energy of the right and left gastrocnemii of Frog 10. As this animal had no lead at any time, we are forced to the conclusion that the diminution in the force of contractile power of the right or stimulated muscle is mostly the result of its damage during fatigue. This is made quite manifest when we consult Section D, Frog 24 (control); here the disparity in muscular power is so slight as to be irrelevant.

FROG 22. WEIGHT 28 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
1/ 5/13	...	15″	8–9	Left gastrocnemius fatigued by indirect method. No symptoms at any time.
1/ 6/13	...	12″	8–9	
1/ 7/13	...	15″	8–9	
1/ 8/13	...	15″	8–9	
1/ 9/13	...	15″	8–9	
1/10/13	...	15″	8–9	
1/11/13	...	15″	8–9	
1/12/13	...	15″	8–9	
1/13/13	0.175	15″	8–9	
1/17/13	...	...	...	Frog died.

FROG 23

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/ 5/13	...	13″	8–9	Left gastrocnemius fatigued by indirect method.
2/ 6/13	...	13″	8–9	
2/ 7/13	...	13″	8–9	
2/ 8/13	...	13″	8–9	
2/ 9/13	...	13″	8–9	
2/10/13	...	13″	8–9	
2/11/13	...	13″	8–9	
2/12/13	...	13″	8–9	
2/13/13	...	13″	8–9	
2/14/13	0.125	13″	8–9	
2/17/13	...	13″	8–9	
2/18/13	...	13″	8–9	
2/24/13	...	...	...	Frog killed.

For curve of work see chart (Fig. 2).
Work: Right gastrocnemius, 276.7 gm. mil; left, 13 gm. mil.

Although in this series the fatigued muscle in the lead-poisoned frog showed considerable diminution in energy, the qualitative difference is not decisive when compared with the control frog. The gastrocnemii of

Nos. 9, 11, 13, 14 and 16 show, respectively, 97.3, 107, 119.2, 125.2 and 127 gm. millimeters of work as against 132 gm. millimeters for control Frog. 10. Since Frog 9 was not killed, post mortem changes can partially account for its decrease, particularly when the opposite leg showed a corresponding change.

FROG 24. NORMAL CONTROL. WEIGHT 32 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/ 5/13	...	13″	8–9	Left gastrocnemius stimulated by indirect method.
2/ 6/13	...	13″	8–9	
2/ 7/13	...	13″	8–9	
2/ 8/13	...	13″	8–9	No symptoms.
2/ 9/13	...	13″	8–9	No symptoms.
2/10/13	...	13″	8–9	No symptoms.
2/11/13	...	13″	8–9	No symptoms.
2/12/13	...	13″	8–9	No symptoms.
2/13/13	...	13″	8–9	No symptoms.
2/14/13	...	13″	8–9	No symptoms.
2/17/13	...	13″	8–9	No symptoms.
2/18/13	...	13″	8–9	No symptoms.
2/24/12	...	...	...	Frog killed.

For results, see curve and plot (Fig. 3).
Work: Right gastrocnemius, 287 gm. mil.; left, 274.5 gm. mil.

FROG 25. WEIGHT 33 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/ 6/13	...	13″	8–9	Left gastrocnemius stimulated by indirect method.
2/ 7/13	...	13″	8–9	
2/ 8/13	...	13″	8–9	
2/ 9/13	...	13″	8–9	
2/12/13	...	13″	8–9	No symptoms.
2/13/13	...	13″	8–9	No symptoms.
2/14/13	...	13″	8–9	No symptoms.
2/15/13	...	13″	8–9	No symptoms.
2/16/13	0.175	13″	8–9	No symptoms.
2/20/13	...	...	...	Frog killed.

Reaction to Induction Shock:
Both gastrocnemii react well at 12 cm.
Work: Right gastrocnemius, 270.5 gm. mil.; left, 39.3 gm. mil.

An analysis of Section D gives an entirely different view. Here most of the results are clear and decisive. There can be no question that the disparity in the contractile power of the muscles of Frogs 21, 23, 25 and 26 is not due to the lead, except as the fatigue facilitates the pathological changes which characterize it.

By reference to the plotted curve (Fig. 1) representing the experiment with Frog 23, it is obvious that its right gastrocnemius was able to do 276.7 gm. millimeters of work. The left, or fatigued gastrocnemius, was able to perform but a scant 13 gm. millimeters of work. It is self-evident that the former is able to do 21.24 times the work done by the latter.

FROG 26. WEIGHT 31 GM.

Date	Amount of Lead, c.c.	Stimulation Amount of	Position of Secondary Coil, cm.	Notes
2/ 7/13	...	14″	8–9	Left gastrocnemius fatigued by indirect method.
2/ 8/13	...	14″	8–9	
2/ 9/13	...	14″	8–9	
2/10/13	...	14″	8–9	
2/11/13	...	14″	8–9	
2/12/13	...	14″	8–9	
2/13/13	...	14″	8–9	
2/14/13	...	14″	8–9	
2/15/13	0.2	14″	8–9	Very slight reflex diminution.
2/16/13	...	14″	8–9	Frog recovered.
2/21/13	...	...	...	Frog killed.

Reaction to Induction Shock:
Both gastrocnemii react well at 12 cm.
Work: Right gastrocnemius, 221.7 gm. mil.; left, 17.8 gm. mil.

FROG 27. WEIGHT 31 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/18/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method.
2/19/13	...	12″	8–9	
2/21/13	...	12″	8–9	
2/22/13	...	12″	8–9	
2/23/13	...	12″	8–9	
2/25/13	...	12″	8–9	
2/26/13	...	12″	8–9	
2/27/13	...	12″	8–9	
2/28/13	0.225	12″	8–9	
3/ 2/13	...	12″	8–9	Slight decrease in reflexes and stupor.
3/ 4/13	...	12″	8–9	Frog killed.

Reaction to Induction Shock:
Both react well at 12 cm.
Work: Right gastrocnemius, 245.3 gm. mil.; left gastrocnemius, 17.9 gm. mil.

In order to eliminate the effect of the stimulation and lead separately, a normal frog of the same weight as No. 23 was given the same amount of stimulation without the lead. This is Frog 24 (Fig. 2). By calculation it is seen that the right gastrocnemius has 287 gm. millimeters of work, while the left or fatigued gastrocnemius has 274.5 gm. millimeters. This leaves a difference of 12.5 gm. millimeters to account for the effect of fatigue in a normal frog, and 10.3 gm. millimeters for the effect of the lead. These are insignificant differences, particularly the 10.3 gm. millimeters which could be physiologic in character.

FROG 28. WEIGHT 30 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
2/16/13	...	13″	8–9	Left gastrocnemius fatigued by indirect method.
2/17/13	...	13″	8–9	
2/18/13	...	13″	8–9	
2/19/13	...	13″	8–9	
2/20/13	...	13″	8–9	
2/21/13	...	13″	8–9	
2/24/13	...	13″	8–9	
2/25/13	...	13″	8–9	
2/26/13	0.25	13″	8–9	
3/ 2/13	...	13″	8–9	Frog killed.

Reaction to Induction Shock:

Both gastrocnemii react well at 12 cm.

Work: Right gastrocnemius, 195.6 gm. mil.; left, 19.8 gm. mil.

FROG 29. WEIGHT 33 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
3/ 3/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method.
3/ 4/13	...	12″	8–9	
3/ 5/13	...	12″	8–9	
3/ 6/13	...	12″	8–9	
3/ 7/13	...	12″	8–9	
3/ 8/13	...	12″	8–9	
3/ 9/13	...	12″	8–9	
3/10/13	...	12″	8–9	
3/11/13	...	12″	8–9	
3/12/13	0.3	12″	8–9	Slight stupor.
3/14/13	...	12″	8–9	Recovered fully.
3/15/13	...	12″	8–9	
3/16/13	...	12″	8–9	
3/16/13	...	12″	8–9	
3/20/13	...	...	...	Frog killed.

Reaction to Induction Shock:

Both gastrocnemii react well at 12 cm.

Work: Right gastrocnemius, 203.6 gm. mil.; left, 21.7 gm. mil.

FROG 30. WEIGHT 32 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
3/ 8/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method.
3/ 9/13	...	12″	8–9	
3/10/13	...	12″	8–9	
3/11/13	...	12″	8–9	
3/12/13	...	12″	8–9	
3/13/13	...	12″	8–9	
3/14/13	...	12″	8–9	
3/15/13	...	12″	8–9	
3/16/13	...	12″	8–9	
3/17/13	0.35	12″	8–9	Well developed stupor followed Pb. injection.
3/20/13	...	12″	8–9	Frog recovered only partially; at times fairly irritable; at other times listless.
3/21/13	...	...	...	Frog killed.

Reaction to Induction Shock:

Direct application:

Right at 12 negative; at 11.5 positive.

Left at 11 negative; at 10.5 positive.

Work: Right gastrocnemius, 183; left, 21.2.

FROG 31. WEIGHT 29 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
3/15/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method.
3/16/13	...	12″	8–9	
3/17/13	...	12″	8–9	
3/18/13	...	12″	8–9	
3/19/13	...	12″	8–9	
3/20/13	...	12″	8–9	
3/21/13	...	12″	8–9	
3/22/13	...	12″	8–9	
3/23/13	...	12″	8–9	
3/24/13	0.45	12″	8–9	Marked stupor and reflex diminution following Pb. injection. Recovery only slight, and then seemed to grow progressively worse.
3/28/13	...	...	...	Frog killed.

Reaction to Induction Shock:

Direct application:

Right gastrocnemius at 10 negative; at 9 positive.

Left gastrocnemius at 8 negative, at 7 positive.

Work: Right gastrocnemius, 141.3 gm. mil.; left, 15.4 gm. mil.

Frogs 29, 30, 31 and 32 show the effect of increasing dosage by producing stupor and diminution of reflexes. The confusion in the results of the quantitative work is also noted. Although the fatigued muscle shows a very marked decrease in energy, the unfatigued muscle is also affected so markedly that one is at a loss to know how much to attribute to fatigue and how much to the lead itself. This confusion is averted in the frogs referred to above.

In this work, two methods of fatigue were used. First, a direct application of the electrodes to the muscles, and second, an electrical irritation of the skin which produced a muscular contraction resulting from the frog's attempt to get away from the irritation. This was accomplished by an apparatus which I devised for the purpose, the details of which appear later.

FROG 32. WEIGHT 32 GM.

Date	Amount of Lead, c.c.	Amount of Stimulation	Position of Secondary Coil, cm.	Notes
3/20/13	...	12″	8–9	Left gastrocnemius fatigued by indirect method.
3/21/13	...	12″	8–9	
3/22/13	...	12″	8–9	
3/23/13	...	12″	8–9	
3/24/13	...	12″	8–9	
3/25/13	...	12″	8–9	
3/27/13	...	12″	8–9	
3/28/13	...	12″	8–9	
3/29/13	...	12″	8–9	
3/30/13	0.53	12″	8–9	
3/31/13	...	...	...	Marked stupor which grew progressively worse. Reflexes also diminished markedly. Frog will probably not recover.
4/3 /13	...	...	...	Frog killed.

Reaction to Induction Shock:
Direct application:
Right gastrocnemius at 7 negative; at 6 positive.
Left gastrocnemius at 4 negative; at 3 positive.
Work: Right gastrocnemius, 75.4 gm. mil.; left, practically *nil*.

The first method was fairly successful in the gross, but was a complete failure when accurate methods were used. This is clearly shown by the experiments in Section C of the Protocol of Experiments. The reasons for the inefficiency of this method have already been explained. The abandonment of this method resulted in the adoption of another, which makes use of an apparatus which the subjoined diagram will render obvious (Fig. 3).

Tension is put on the left leg of the frog by anchoring it to the binding post P. A piece of twine is used which is about an inch long.

It is not well to have it longer, as too much freedom of motion obtains. Some suitable electrode is placed adjacent to the tendon of the gastrocnemius at A, the height of the electrode being regulated by a piece of tin-foil which supports it at T F.

One electrode is fastened to the front leg of the frog by a curved copper wire, and the current is closed by the contact of the electrode with the tendon of the gastrocnemius. The resulting irritation causes a sudden contraction of the leg and thigh muscles, which break the circuit by the withdrawal of the leg from the electrode. The gastrocnemius is invariably contracted by this movement, as can be evidenced by palpation. The break in the circuit almost instantly permits the leg to drift back on the point of the electrode when the contraction is repeated. In a normal 25-gm. frog, this rate may run from three to four per second,

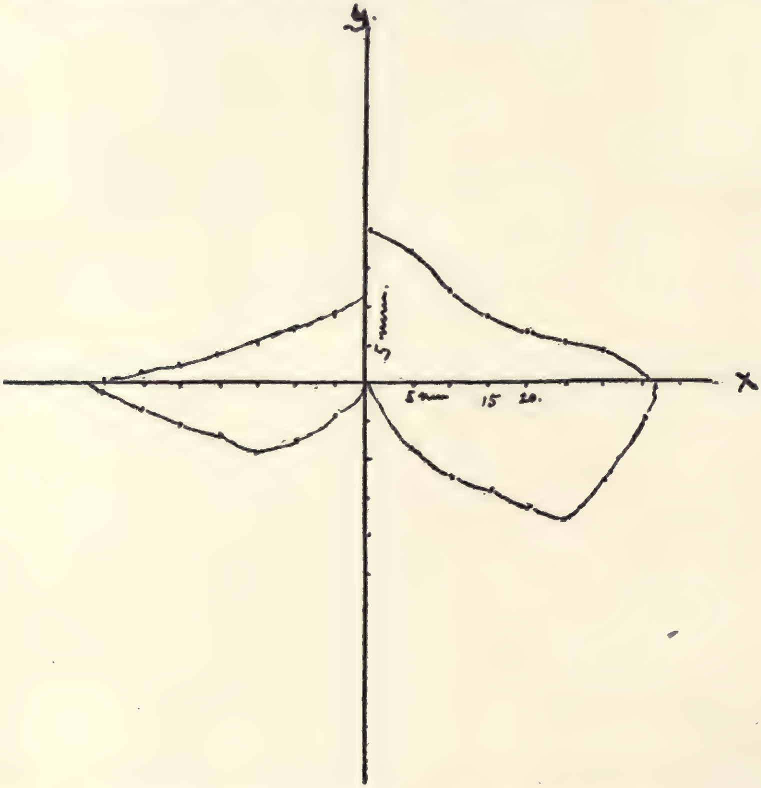

Fig. 1.—Explanation of Plotted Curves. (Frog 23.) The curves represent the type of results derived from the indirect form of stimulation in a lead frog. The abscissa and ordinate are ruled off in spaces of 5 mm. each. To the right of the ordinate Y is represented the curve of lift and curve of work of the right gastrocnemius. The former is above the abscissa, and the latter below. To the left of the ordinate is represented the curves of lift and work of the left gastrocnemius. The disparity shown between the two curves of work and lift is not absolute, as those for the left leg are magnified ten times.

but it is not long before the rate becomes rapidly decreased to one or two per second.

It is entirely self-evident that the greatest advantage accruing from this simple device is the one which makes use of fatigue of muscles by mechanical means, even though the induction coil is used as the exciting factor.

This method besides being admirably adapted to our purpose, in that it imitates fairly perfectly the actual contraction of human muscles in doing work, requires no additional apparatus. The pure electrical form of stimulation, even when perfect, is open to the objection that it does not parallel closely the mechanical form used by man in his labor. Its applicability to our proposition is well illustrated by the fact that muscles of a normal frog do not lose perceptibly in power when stimulated in this way, when sufficient time is given for recovery from the fatigue induced.

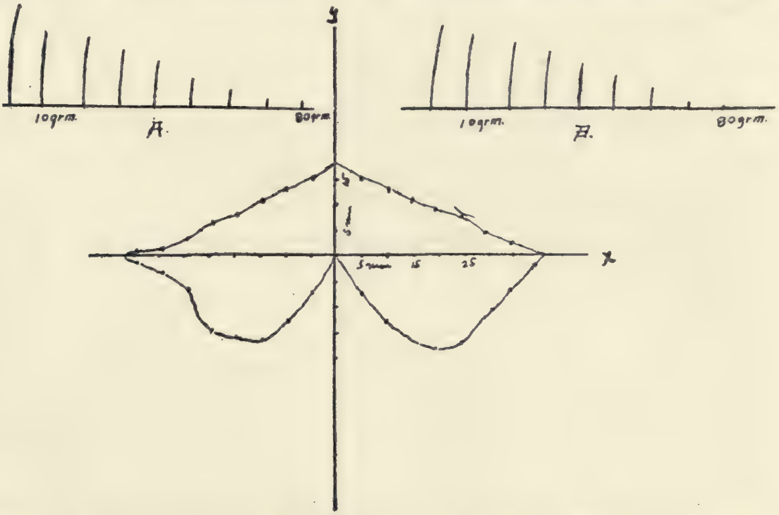

Fig. 2.—Explanation of Plotted Curve. (Frog 24.) The curve represents the results obtained by the indirect form of stimulation in a control frog which had received no lead. The curves to the right of the abscissa represent the right leg, and those to the left, the left leg. There is no magnification of any curve on either side. Tracings A and B represent the excursion of the left and right gastrocnemii muscles, respectively, under stimulus of a weak induction shock, and weighted with loads of from 10 to 80 grams.

The experiments showed the importance of the administration of a subphysiological dose of lead. Good results were almost always obtained when the doses were not so large as to produce stupor and marked diminution of reflexes to mechanical and electrical stimulation. In case this caution is not observed, the non-stimulated as well as the stimulated muscles show loss of power.

As in all work of this nature, a terminal recovery interval should be observed. In order to determine whether the loss of power in a muscle is permanent, the effects of ordinary fatigue should be permitted to disappear. In muscles fatigued only once a day, forty-eight to seventy-two hours suffice admirably for such restoration. Possibly less time would do, but a generous margin was left so it would not be possible to account for the loss of power in the lead frog from the effects of the stimulation.

SUMMARY

1. That the quantitative differences between the amount of work done by the fatigued and non-fatigued leg in a lead-poisoned frog is not conclusive when the direct application of the electric current is used for muscle fatigue.

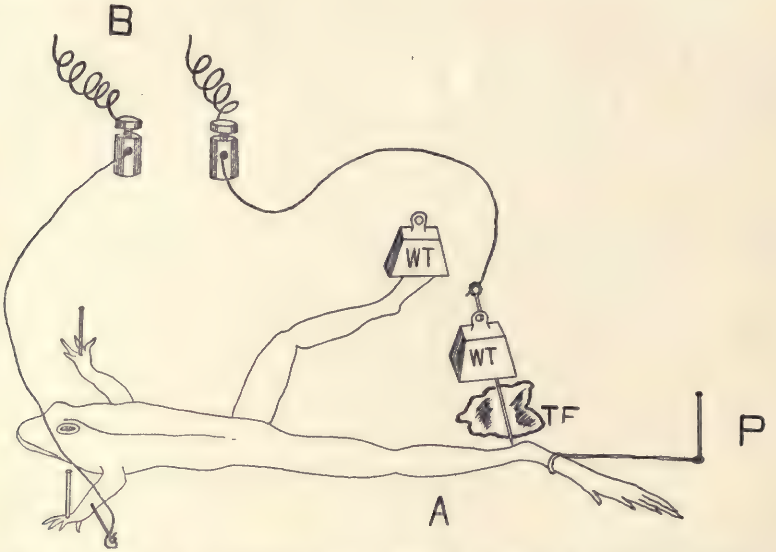

Fig. 3.—Diagram representing the indirect method of inducing fatigue of muscle. For explanation see text.

2. No conclusive quantitative differences are observed where large enough doses of the metal are given to produce stupor and marked diminution of reflexes.

3. That these experiments, as worked out by the indirect method of fatigue production, are conclusive evidence of the validity of Edinger's contention, viz., that lead in itself has no predilection for any group of muscles except as that choice is made possible by their over-use. Fatigue is, therefore, the main factor in the localization of lead palsies.

The Harvard inductorium, manufactured by the Harvard Apparatus Co., was used in all the experiments. The battery was a single Columbia dry cell.

Acknowledgement is made to the Department of Physiology, to Dr. Lombard, Dr. Cope and Mr. F. T. Munson for apparatus loaned me; and to Dr. Warthin for the suggestion of the problem and his control of the investigation.

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REPRINTED FROM INTERNATIONAL CLINICS, VOL. IV, SERIES 23, 1913

TRAUMATIC LIPÆMIA AND FATTY EMBOLISM

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I. INTRODUCTION

The entrance of free liquid fat into the blood stream as a result of trauma affecting the bone-marrow or the panniculi has become, through the freedom from infection gained by modern surgical technic, the most serious complication attending such injuries, and is a very common occurrence. It is highly probable that in every case of amputation or fracture of the long bones some fat is set free from the ruptured fat-cells and, either directly or by way of the lymphatics, enters the blood stream to cause a fat-embolism in the pulmonary capillaries, or, passing the lungs, in the capillaries of some other organ. When the amount of fat liberated is small, as it is in the majority of cases of bone injury, the results of such a fat-embolism may be unimportant and unnoticed; but it is evident that the gravity of the condition will depend upon the anatomical importance of the capillaries blocked by the fat-emboli. A very small amount of fat passing through the lung capillaries to lodge in certain capillaries of the brain may cause severe or even fatal disturbances; on the other hand, a relatively large amount of fat may be lodged in the pulmonary capillaries without causing great damage.

The amount of free fat liberated into the blood stream is often almost incredible, single sections of the various organs and tissues of the body showing, on microscopical examination, such numerous emboli that it would seem that the total amount of fat contained in the emboli must far exceed the fat-content of the injured bone. In some of these cases when the entire circulatory system is apparently flooded with fat, the injury to the bone and bone-marrow may apparently be very slight, although in severe cases one or more comminuted fractures are usually present. Concussions, amputations (even when most carefully and perfectly performed), incomplete fractures, osteomyelitis, crushing or infection of the subcutaneous panniculi, laceration of fat-tissue by dislocations or efforts to replace dislocated bones, rédressement, brisement forcé, pressure upon atrophic bones, injuries to adipose tissue during labor or delivery, crushing of fat-cells of the panniculi during surgical operations, rupture of a fatty liver, purulent inflammation of fatty tissues, burns of the skin, etc., are the chief etiologic factors of traumatic lipæmia, in addition to the more direct lesions of the marrow following complete fractures. The lipæmia and fat-embolism resulting from any one of these causes may be slight or marked, without symptoms or with severe ones, terminating favorably or fatally. There is no clinical correspondence between the apparent injury and the degree of the resulting lipæmia. Injuries apparently identical may in one individual be followed by a fatal lipæmia, while in another not the slightest disturbance attributable to fatty embolism can be perceived.

The symptoms of traumatic lipæmia not only vary according to the degree and location of the emboli, but are of such a nature that the condition is rarely recognized before autopsy. The total number of cases reported is about three hundred and fifty, and the majority of these are not so clearly defined as to place them beyond doubt. In only about one-half of the number were thorough pathologic studies made. In autopsy and microscopic examinations important details are lacking, and strict analysis would exclude many of them. It is significant that eighty-six of the reported cases were observed in the seventeen years following 1862, when Zenker discovered fatty embolism,—a period when interest in the condition was still fresh. Except in Germany, few cases of fatal traumatic lipæmia have recently been observed, and the condition is regarded by the average surgeon as rare. In this country, particularly, there have been few records of its occurrence, and it is reasonable to infer that a correspondingly small number of diagnoses has been made. Most of the reports upon fatty embolism are found in German literature; and until recently these articles in the main pertained to its etiology and pathology; but within the last five years more attention has been paid to diagnosis and treatment. The text-books on general surgery give a general impression that fatty embolism is a pathologic curiosity rather than a condition of practical interest, although its serious nature is usually admitted. The subject is either inadequately treated, or is discussed in general stereotyped statements. Scriba's monograph, published in 1880, forms the basis of these articles, even of the most recent; and his statement—an incorrect one, as shown by all recent work—that the temperature is lowered in fatty embolism—is perpetuated in the most recent English and American text-books on surgery. Meagre descriptions are given of its pathology, and the possibility of an antemortem differential diagnosis is usually not considered. It follows that in the failure to establish a diagnosis therapeusis must also be in vain. The therapeutics of fatty embolism recently formulated by Wilms and others have as yet been incorporated into few of the surgical text-books and systems. The time has come that more attention should be paid to this sadly-neglected branch of surgery, and that *the occurrence of fatty embolism after any injury to the bones be at least regarded as a possibility, and that preventive measures be instituted, or therapeutic efforts be made, whenever there is a suspicion of its occurrence.*

The medicolegal significance of fatty embolism is also great, but is wholly disregarded at the present time in this country. As it is a cause of death from apparently slight as well as more serious injuries to bones and soft parts, the necessity of recognizing its occurrence by means of properly-performed autopsies must be strongly emphasized. Fatal cases of fatty embolism from the common accidents of our large cities are every day diagnosed as "shock, coma, apoplexy, alcoholism, concussion, 'bad heart,' etc." In some of these cases the proper responsibility may be placed; but in others, of which I have personal knowledge, the responsibility for accidental and criminal violence was not placed because of the diagnosis incorrectly made by an ignorant coroner and coroner's physician. There should be further study and investigation of certain medicolegal aspects of fatty embolism; its postmortal appearance, its occurrence in burns of the skin, antemortem or postmortem, etc. The question of the thymicolymphatic constitution also crops up here, inasmuch as some writers affirm that there is an especial susceptibility to lipæmia and fatty embolism, to be explained by the assumption of the existence of such a diathesis.

In the writer's opinion, fatty embolism resulting from traumatic lipæmia is an important surgical condition, which is not of rare occurrence but is probably, at the present time, in the absence of infection, the most frequent cause of death after fractures of the long bones. According to Gröndahl, fatty cerebral embolism is responsible for one per cent. of the deaths following bone injuries. It is apparently not an uncommon experience for surgeons to lose patients suffering from fractures or amputation within a few days after proper treatment had been given, and when all the conditions seemed favorable. Without warning, and without apparent cause, a state of restlessness, with mental anxiety, disturbance of heart and respiration, delirium, and coma, sets in, and death may take place within twelve to twenty-four hours. In explanation and justification of these fatal cases, the surgeon frequently takes refuge behind a diagnosis of shock or concussion. It is extremely probable that the majority of these cases are the results of traumatic lipæmia and fatty embolism, and it is highly desirable that more attention be paid to the differential diagnosis of fatty embolism, shock, concussion, diabetic coma, lymphatic struma, alcoholism, etc. In a relatively small postmortem service of 560 autopsies, the writer saw twelve fatal cases of traumatic lipæmia and fatty embolism, nine of these following fracture of the long bones, one occurring as the result of damage to adipose tissues received during labor and delivery, and another following a surgical operation for removal of a mammary cancer, and in one case of fatal burn of skin. Fatty embolism of the liver without pulmonary emboli was seen in a case of pituitary infantilism and adipositas following operation and prolonged chloroform narcosis. The most significant thing about these cases is the fact that very few accident cases come into this pathological service, and of the fracture cases terminating fatally and examined postmortem *all showed a marked fatty embolism as the cause of death.* In only one of these twelve cases had the condition been diagnosed clinically before death. Shock, heart-failure, acute cardiac dilatation, cerebral hemorrhage, pneumonia, sepsis, insanity, and alcoholism were the clinical diagnoses for the other cases, and the true cause of the symptoms remained unsuspected. Since these occurred in the practice or hospital service of clinicians of the highest standing, this general failure to recognize the condition can be taken only as an indication of its unsatisfactory status clinically. It has, therefore, seemed advisable to make a detailed study of these cases with the purpose of emphasizing the surgical importance of traumatic lipæmia with resulting embolism, and, if possible, to extend the knowledge of its pathology and symptomatology.

Along both of the latter lines the research has been successful. A new clinical sign, *the presence of free fat and fat-granule alveolar cells in the sputum,* is the earliest positive evidence of the condition, being detected even before the appearance of free fat in the urine. The presence of fat-emboli in all of the organs and tissues of the body and the resulting pathological changes have been thoroughly studied, and new points in the general pathology determined,—thus new light is thrown upon the symptoms and the cause of death. Incidentally, new facts have been gained concerning fatty degeneration and the ability of different organs to take up fat.

II. HISTORICAL SURVEY

The history of lipæmia and its effect upon the circulation begins with the experimental work of Magendie during the years 1821–1836. While he had no knowledge of the occurrence of a pathological fatty embolism in man, *Magendie*[1] performed many experiments upon animals to determine the effects of the injection of oil into the circulating blood, and discovered that the fluid fat would not pass the smaller vessels, but blocked them mechanically. This obstruction of the capillaries he referred to an increased viscosity of the blood; and, without thinking of the possible occurrence of fatty embolism in man, he passed over this more immediate and logical deduction to the conclusion that in fevers, severe sweating, etc., the increased viscosity of the blood would lead to the formation of numerous capillary emboli, that would in turn cause pneumonia and inflammation of other organs. Magendie's descriptions of the experimental introduction of liquid oil into the venous circulation are classics for this particular field of experimental pathology and physiology. He described the symptoms resulting from small and large intravenous injections of olive oil, noted the dyspnœa, fever, râles, etc., portrayed the pathological changes in the lungs, and noted the presence of oil in the blood-vessels and alveoli of the lungs.

As early as 1669 *Lower*[2] had injected milk in large amounts intravenously into dogs, and this fact, with similar observations in the earlier literature, is sometimes referred to as the beginning of our knowledge concerning fat-embolism. *Virchow*[2] in 1862, *Schwick*[3] in 1864, and *Weber*[4] in 1865 showed that the experimental injection of emulsified fat in milk, pus, etc., was not followed by embolism. Other observers verified these conclusions, but the true explanation of the failure to produce fatty emboli through injections of minutely-emulsified fat has been frequently overlooked.

Virchow made repeated experiments with intravenous injections of oil, and noted the resulting dyspnœa after injecting a certain amount. When a larger injection was given, and the animal died, he found on autopsy an acute œdema of the lungs, the air-spaces being entirely filled with foamy serum. He noted the injection of the pulmonary capillaries with fat. He also verified the experimental work of *Gluge* and *Thiernesse*,[6] who had claimed to be able to produce a fatty pneumonia and fatty liver and kidneys by intravenous injections of fat and by fat-feeding, but he was unable to confirm their results, and explained the fatty pneumonia as the result of oil entering the lungs through the trachea. After injections he found fat-emboli in the liver and kidneys, but no fatty infiltration of the parenchyma.

Frerichs[7] injected oil into the portal vein of dogs, and found that it did not pass the liver, but remained in that organ and was gradually taken up by the liver-cells, giving the appearance of a fatty infiltration.

H. Müller, in 1860,[8] was the first to observe fatty embolism in man while examining the eyes of a young man dying from chronic nephritis and who had suffered from amblyopia before death. In the choroidal capillaries of about 0.06 mm. diameter he found slender homogeneous plugs made up largely of free fat, partly in drops and partly in the form of granules. Müller thought that these emboli arose either from atheromatous foci in the ciliary arteries or from a cardiac thrombus. In the same year *B. Cohn*[9] observed fatty emboli in the capillaries of the brain and extremities in man, and regarded them as due either to fatty degeneration of the vessel wall or of the tissue surrounding it, or to the rupture of an atheromatous focus in some larger vessel. Neither Müller nor Cohn attached any pathological significance to these fatty emboli, but regarded them as accidental findings.

In 1862 *Zenker*[10] observed the first case of fatty embolism of the pulmonary capillaries in man. A railroad laborer was crushed between two buffers, and died shortly after. The autopsy revealed multiple fractures of the ribs, and laceration of the liver and stomach. The pulmonary capillaries were found to contain great numbers of emboli of fluid fat. Zenker thought the fat came from the stomach contents as the result of aspiration by the gaping hepatic veins. *Wagner*,[11] in the same year, reported two cases of pyæmia, one with caries of the pubic bone, both showing multiple fatty emboli in the pulmonary capillaries and in the vessels of the kidneys and heart. He believed that the fluid fat most likely entered the blood stream from an older abscess, and then, lodging in the capillaries of the lung and systemic circulation, produced metastatic abscesses. He reports four other cases of pulmonary fat-embolism, two of them being combined with pyæmia.

Grohe,[12] in a critical abstract of Wagner's work, suggested that the fatty emboli might arise from an agonal confluence of the fat normally present in the blood stream. *Lancereaux*[13] reported the presence of fat-emboli in the cerebral capillaries of a patient who had Bright's disease. He thought that the fat in the emboli might be attributed to fatty degeneration of the capillary walls.

During the years 1863–4–5 a number of dissertations and articles appeared, giving the results of the experimental study of various phases of the problem of fatty embolism. *Bergmann*,[14] working with cats, found that injections of fat into the venous circulation caused obstruction of the pulmonary capillaries and produced great circulatory disturbances. He observed also that a portion of the fat passed through the pulmonary circulation, causing emboli in the liver, kidneys, and other organs, but it was in part excreted through the urine. He noted also that the fat in the emboli was not permanently fixed there, but that a part of it passed through the vessel wall into the neighboring tissues. He observed the rupture of the pulmonary capillaries, and the escape of blood and fat into the alveolar spaces. The presence of fat-droplets in the kidney tubules he attributed to the rupture of the distended glomerular capillaries. While he did not consider fatty embolism as an important primary pathological condition, he regarded it as a serious complication which might cause death through cardiac paralysis and pulmonary œdema.

Hohlbeck[15] carried out similar experiments on horses. In five animals experimented upon, intravenous injections of relatively large amounts of fat caused slight difficulty in breathing in three, coughing and dyspnœa in one, and marked emaciation in the other. All showed at autopsy hemorrhagic infarcts of the lung, lobular pneumonia, and numerous fatty emboli. The alveolar spaces also contained numerous epithelial cells showing marked fatty degeneration.

At this time appeared the work of *Weber* and *Schwick*, referred to above. These observers found that injections of pure oil into the veins caused fatty emboli, but that emulsions of fat produced no emboli. Areas of hyperæmia were found in the lungs, brain, spleen, liver, and kidneys, and these they regarded as the main pathologic conditions resulting from such embolism. They did not consider the condition in man a dangerous one.

Wagner[16] reported forty-eight cases of fatty embolism seen in man. Of these, fifteen were cases of complicated or infected fractures, twelve were acute suppuration of bones, fifteen were severe injuries to bones or soft parts quickly resulting in death, and six were chronic suppuration of different tissues. On finding numerous fat-droplets in a vein after an amputation for a complicated fracture, he believed that he had discovered the path of the fat from the periphery to the right heart. By experiments upon dogs he demonstrated that injuries to the bone-marrow soon produced fatty emboli in the lungs. Only after acute fractures were pure fat-emboli formed. Contaminated fat masses from old purulent foci gave rise to metastatic inflammations. Death might, however, ensue from hyperæmia and œdema of the lungs before the abscesses developed.

Uffelmann[17] reported two cases of pyæmia with numerous fatty emboli in the pulmonary capillaries, and upheld the view that emboli composed of non-irritating substances did not produce infarcts.

Weber[18] opposed the view that metastatic abscesses could be produced by fatty emboli. The entrance of a moderate amount of fat into the blood caused hyperæmia in the neighborhood of the embolus; larger amounts quickly resulted in death.

Roser[19] called attention to the fact that, in fresh complicated fractures, fat-droplets often flowed from the wound during the first few days. In a case of osteomyelitis he found, on cutting through the periosteum, a collection of bloody serous fluid rich in fat-droplets. He explained this as the result of a high pressure within the medullary canal which forced the fat of the marrow through the Haversian canals to collect beneath the periosteum. A similar collection of fluid fat was seen by *Gosselin*[20] about the knee-joint after crushing of the soft parts. Such collections of free fluid fat in the tissues may well serve as the source of fat which finds entrance to the vessels.

Busch[21] also took up the problems of fat-embolism from an experimental standpoint. As the result of numerous experiments he drew the following conclusions: Following destruction of the marrow there was always fat-embolism of the smaller vessels and capillaries of the lung without appreciable lesions of the pulmonary tissues. The fat was taken up by the torn and gaping vessels of the injured bone, and in a lesser degree by the lymphatics. The absorption of the fat may be so rapid that fat-emboli may be demonstrated in the pulmonary capillaries within a few minutes after the injury. Inflammation and metastatic abscesses are not caused by the fat-emboli. Collateral hyperæmia and hemorrhage occur only when the fatty embolism is very marked; and only in such cases can the condition be fatal.

Fischer[22] first called attention to fatty embolism following fractures caused by bullets. *Waldeyer*[23] reported a case of osteomyelitis of the leg with extensive thrombosis of the veins. Numerous fat-droplets were present in the thrombus, and *Waldeyer*[23] inclined to the view that the pulmonary fat-emboli present arose from the degenerating thrombus rather than from the marrow.

Buttlewsi[24] is quoted by Park as one of the early observers of cases of fatty embolism. The original article is not accessible.

Joessel,[25] *Mulot*,[26] and *Feltz*[27] reported cases of fatty embolism without enriching our knowledge of the subject. Mulot observed a case in which fatty embolism followed the freezing of both feet.

Niederstadt[28] and *Klebs*[29] also called attention to the occurrence of fatty embolism in osteomyelitis. *Cohnheim*[30] held that a fatty embolus in a capillary could not in itself produce an extravasation, but that, when the emboli were numerous, infarcts could be produced as the result of purely mechanical factors.

Egli[31] found fatty emboli in two cases of cardiac thrombosis undergoing puriform softening and fatty degeneration.

Lücke[32] reported a case of subcutaneous fracture of the leg followed by death on the second day; numerous fatty emboli were observed in the lungs. Fat-droplets were found in an extravasation in the *tibialis antica*, also in the popliteal vein and in the right auricle.

Bergmann[33] was the first to make a diagnosis of fatty embolism during life; this was in a fatal case following fracture of the femur.

Wille[34] saw three cases of pulmonary emboli of fat without perceptible change in the parenchyma of the organ.

Czerny[35] studied fat-embolism, particularly from the clinical side, with reference to changes in temperature, pulse, respiration, etc. He concluded that the symptoms were variable, and that the diagnosis must eventually rest upon a known cause of fatty embolism. The latter can be regarded as a cause of death only when the emboli are found in important organs, such as the brain, heart, etc., or are sufficiently numerous to cause significant functional disturbances.

Küttner[36] held that fatty emboli could cause infarcts only when an extensive fatty embolism of the lung is present.

Schwenninger[37] reported two autopsies in cases of fatty embolism. In one death occurred three hours after the crushing of both legs; numerous fatty emboli were found in the lung capillaries. In the second case death took place after six hours, and the autopsy showed numerous fat-emboli, and an extreme œdema of the lungs.

Halm,[38] after examination of twenty-one cases of bone injury and experimental work upon animals, concluded that all injuries to bones caused fatty embolism. He observed no inflammation nor infarction of the lung. He describes fully the symptoms of fatty embolism, and notes the occurrence of fat-droplets in the urine. In the pulmonary areas obstructed by emboli he found anæmia, and in the free portions hyperæmia. He could find no fat-emboli in animals whose mesenteric and subcutaneous fat had been injured.

Riedel[39] observed fat-embolism in nine cases of fatal bone injury, and in two of injury to the soft parts. He also carried out animal experiments, and concluded that all injury to bones caused fatty embolism, but obtained negative results from injuries to the panniculi. He was unable to prove that fatty embolism always followed osteomyelitis, but concluded that indifferent bodies introduced into the marrow produced much less fatty embolism than did agents which caused irritation and inflammation. He believed that the fat entered the circulation chiefly through the veins. He found no fatty embolism after injections of fat into the pleural cavity. In the lungs he found small hemorrhagic infarcts, œdema, fibrinous exudate, and fatty alveolar cells.

Heschl[40] reported one case due to a complicated fracture of the femur.

Hamilton[41] saw a case of multiple rupture of a fatty liver with marked fatty embolism of the lungs. Some emboli were also found in the kidneys.

Reyher[42] reported three cases of fatty embolism following bullet wounds; in one case the bone was grazed only, the marrow cavity not being touched.

Böttcher[43] also reported a case of fatal fat-embolism resulting from a bullet wound in the knee.

Flournoy,[44] in an examination of two hundred and fifty bodies in the Pathological Institute at Strassburg, found fatty emboli in twenty-five different conditions, only five being traumatic bone lesions. The other twenty cases included acute osteomyelitis, senile marasmus with red areas of degeneration in the bone-marrow, acute inflammation of adipose tissue, multiple contusions of subcutaneous adipose tissues, inflammation of soft parts and of bone, pyæmia, etc. Flournoy also carried out animal experimentation. He made subcutaneous injections of olive oil colored with *Rad. Alcannæ*, but without positive result. Incidentally he showed that fat-emboli could be found in the lungs of rabbits killed by a blow upon the neck. In discussing the pathologic features of fatty embolism, Flournoy decided that the fat entered the blood-vessels as free fluid fat through dilated normal or pathological openings in the wall, aided by some force from behind, probably extravasations of blood. After a certain time the fat-emboli are in part taken up by the surrounding tissues, in part excreted by the urine, while a remaining portion is converted into soap and dissolved. As a result of fat-embolism, Flournoy found hyperæmia, hemorrhages, small hemorrhagic infarcts, and œdema in the lungs. He observed no connection between fatty embolism and pyæmia. He emphasized the frequent occurrence of fatty embolism, believing it to be invariable after fractures, but somewhat less frequent after amputations and resections because of the lesser injury to the marrow and the absence of pressure from behind. Infective osteomyelitis, on the other hand, is probably always combined with it because of the prominence of these two causal factors.

Riedel[45] studied the urine of fracture cases, and found fat in forty-two per cent. He also called attention to the presence of peculiar brown casts in the urine of these cases, and explained them by the assumption that fibrin-ferment passed from the blood extravasation into the blood stream along with the fat.

Egli-Sinclair[46] made a partial review of the cases reported up to 1879, basing his article particularly on Flournoy's work, but published no new observations.

In the same year (1880) *Scriba*[47] critically reviewed all of the reported cases of fat-embolism, added original cases of his own, and conducted extensive animal experiments with the aim of solving the various clinical and pathologic problems appertaining to the condition. Scriba's work was the most complete treatise upon this subject to that date, and since its appearance but little had been added to the symptomatology or pathology of fatty embolism until within the last decade. We do not now accept all of his conclusions, but in the main they stand, and the majority of the statements concerning fatty embolism appearing in our textbooks at the present time are based upon them.

Basing his conclusions upon the study of thirty-four cases, he states that, in the urine of patients suffering from fractures or injuries of the bone-marrow, fat appears very frequently, and usually with a certain regularity. In the cases in which it can be demonstrated with certainty it appears in different stages: the first on the second, third, and fourth days after the injury, the second from ten to fourteen days, and more rarely a third, or even a fourth, period after intervals of from six to ten days. At each appearance the urine contains fat for several days.

As the result of animal experimentation he found that fluid fat injected into the venous stream collected chiefly in the pulmonary capillaries and formed fat-emboli. A smaller part passes through into the arterial circulation, in which it in part forms emboli and is in part excreted by the kidneys. After several days (in man about eight to twelve days after the entrance of the fat into the blood) the emboli become free, particularly in the lung, pass into the greater circulation, and, after a time, make the complete circuit back into the veins, and again into the lungs. This circuit may be repeated many times. Small particles of fat may be taken up by the cells of the splenic pulp. Ultimately the greater part of the fat is excreted through the kidneys. In no other organ but the kidneys does the fat pass through an unaltered vessel wall. This statement in regard to the lungs is, however, given with some reservation. Scriba failed to observe the presence of fat in the sputum.

The action of the fat in the blood Scriba regarded as chiefly mechanical, but perhaps also chemical. He thought the fat could not be regarded as an indifferent body. The brown granular casts in the urine of fracture cases, which were described by Riedel, he did not regard as pathognomonic of fatty embolism, since they occur in other diseases characterized by disturbances of circulation in the kidneys and the presence of granular blood-pigment.

As to the action of the fat upon the heart, he denied the possibility of any serious effect upon this organ, and opposed the theory that sudden death in fatty embolism was the result of cardiac paralysis. Any disturbances in the action of the heart due to fatty embolism he thought could be explained sufficiently by the increased mass of fluid within the right heart. He found no evidences of inflammation associated with fatty emboli in the lungs or other organs, although hemorrhagic infarctions were numerous. He concluded that pure fat-emboli must be classed with the so-called bland or non-irritating emboli. Infarcts were found in these cases in which the animal lived at least twelve hours after the injection, but not when the periods were shorter. About old infarcts due to fatty emboli no trace of inflammation was found. He concluded that fat-emboli constantly produce infarcts in the lungs when, through the blocking of a large number of capillaries in a given area, there results so severe a local ischæmia that the anæmic area dies.

In some of the animals experimented upon a general pulmonary œdema was found; occasionally it was only partial, or there was merely an increase of fluid in the pericardial or pleural sac. Scriba would refer the extensive pulmonary œdema seen in human cases of fatty embolism to an irritation of vasomotor centres resulting from the arterial anæmia following the embolism, also to deficient oxygenation of certain areas of the central nervous system. He considered the pulmonary œdema in fatty embolism to be an agonal phenomenon, and not the direct cause of death. The obstruction of the glomerular capillaries and the resulting retention of fluid he thought might also be a factor in the causation of pulmonary œdema.

In the kidneys he found stasis-hyperæmia and ecchymoses in addition to the fat-emboli. The liver contained numerous emboli and presented a marked passive hyperæmia. The cells of the peripheral portion of the lobules often showed abundant fat-droplets, and frequently the cells of the central zone of the lobule exhibited a similar fat-infiltration. In the spleen were found marked passive congestion, numerous capillary emboli, minute round hemorrhages, and occasionally large oil drops which were visible to the naked eye. Many of the pulp-cells contained fat-granules and droplets within their protoplasm.

Scriba regarded the findings in the brain and spinal cord as the most important of all. Passive congestion, arterial and capillary anæmia, perivascular hemorrhages, capillary apoplexies, and small foci of degeneration were found in both brain and cord. In a few experiments the ventricles contained serous, or a bloody serous, fluid associated with a slight degree of œdema of the brain substance. The fat-emboli were most frequent in the pia-vessels, the tela and choroid plexus. Scriba noted also fatty emboli with capillary apoplexies in the mucosa of the stomach, intestine, and bladder, choroid, retina, heart muscle, skeletal muscles, skin, etc., without other noticeable pathologic changes.

He confirmed the statements of others to the effect that fluid fat passes into the venous circulation after every injury to fatty marrow, either through fractures or primary injury to the marrow. The production of fatty embolism by injury to the subcutaneous or intermuscular fat he could not confirm by his experiments. Out of 177 cases of fatty embolism collected by Scriba, in only fourteen instances could the fatty embolism be regarded as the cause of death, and some of these he regarded as doubtful. He therefore concluded that pure fatty embolism can only rarely be fatal. Since the amount of fat entering the veins in human cases is relatively much less than that injected experimentally into animals, Scriba does not believe that pulmonary fat-embolism in man can ever be so extensive as alone to cause death. On the other hand, he thinks that emboli in the central venous system may very frequently result in death. In support of his view that cerebral embolism is the cause of death, Scriba holds that the symptoms of collapse, weakness, apathy, disturbance of consciousness, subnormal temperature, coma, vomiting, paralysis, lessened sensibility, loss of reflex excitability, sense of pain, etc., all point to cerebral embolism. A further symptom-complex is found in the dyspnœa, etc., due to pulmonary embolism. Scriba regards the occurrence of fever as evidence that fatty embolism is not the cause of death. In this he is opposed by all recent investigators. As the most important clinical sign he emphasizes the occurrence of fat in the urine. Next to this he places transitory attacks of dyspnœa, fall of temperature, occasional slight hæmoptysis without fever or marked physical signs, irregularity of the heart, collapse, paleness of the skin, Cheyne-Stokes respiration, convulsions, cramps, and loss of reflex excitability.

Déjerine[48] reported two cases after fractures. In one case crushing of the lower portion of the leg was followed by death within two and a half hours. The pulmonary capillaries were found filled with fat. In the other case fracture of the right parietal bone was followed by death within thirty-six hours. The pulmonary vessels were filled with fat; other organs were not examined. Later Déjerine carried on experimental work, obtaining results differing from those reported by Flournoy and Halm. He did not succeed in producing fatty embolism by fracture of the skull or the extremities, and could cause it only when a marrow cavity was irritated by some foreign body. In his experiments he used laminaria tents.

Von Recklinghausen[49] noted the occurrence of fatty degeneration of the myocardium in fatty embolism, and called attention to its importance.

Wiener[50] believed that in the great majority of cases fat-embolism was a perfectly harmless process. The rapidity of the excretion of the fat he attributed wholly to the power and energy of the heart action. He observed no disturbances of nutrition in the tissues of the brain, kidneys, spleen, muscles, etc., and concluded that only in extremely rare cases could fatty embolism reach such a high degree as to be fatal.

Sanders and Hamilton[51] reported a case of lipæmia and fatty embolism in a man, aged twenty-four years, dying of coma and extreme dyspnœa. Fat-emboli were found in the capillaries of the lungs and kidneys. None were seen in the brain. They regarded the fat-embolism as the cause of death.

Southam[52] reported the case of a man, aged forty, with a compound comminuted fracture of both legs at the lower third. Amputation was performed. On the following day the temperature rose to 103°, the patient became restless and excited, cyanotic, with marked dyspnœa, and died thirty-five hours after the operation. Sections of the lungs showed a marked fatty embolism.

Jolly[53] observed three cases after simple mechanical injury of the subcutaneous panniculus, as the result of self-inflicted bruises produced in patients violently insane. He reports also the two cases earlier reported by Fitz and Flournoy.

Moullin,[54] in twelve out of fourteen cases examined, found fat-embolism of the lungs and kidneys. Seven of these were fracture cases; the other five were respectively pyæmia following acute periostitis, necrosis of fibroid tumor of uterus after abortion, ovariotomy, removal of sequestra, and dislocation of the hip with much laceration of fat-tissue. In one case fatty emboli were found in the lung, although the man had been instantly killed by fracture of the spinal column. No examination of the brain was made in any of these cases. He refers to a case observed by *Fagge* in which fatty embolism followed a primary amputation.

Saundby and Barling[55] found pulmonary fat-emboli in nine cases of severe wounds and injuries fatal within two days. They also saw fat-droplets in the clots of a diabetic with milky blood. They refer to a case of farcy observed by Bendall, in which fat-emboli were also seen.

Minnich[56] called attention to the rarity of fatty embolism in children, and explained this by the small fat-content of their bones. He found fat-embolism in all cases of fracture of the long bones, even when the bones were small, and poor in fat-content.

Skirving[57] reported a case in a healthy man of forty who suffered a compound fracture of both bones of the leg. Next day, while conversing, he became unconscious. Respiration was regular; a few râles were heard at the base of the lungs. Urine contained granular casts and oil-drops. Temperature rose to 104°, respirations 60; patient became cyanotic, died on third day, temperature rising to 105.8° after death. Autopsy showed fatty embolism of lungs and kidneys, and punctiform ecchymoses under endocardium. The brain was not examined.

Pinner[58] observed a case of fracture of the fibula, with small skin wounds and extensive laceration of the skin of leg and thigh. Patient died on the third day. Autopsy showed many fatty emboli in the lungs, fewer in the kidneys, and marked œdema of the lungs.

Zwicke[59] reported two cases. One, a man of twenty-seven, had a subcutaneous fracture of the neck of the femur. On the next day restlessness and tremors of the hands and tongue developed, the symptoms resembling the onset of delirium tremens. Died on fourth day at beginning of chloroform anæsthesia. Lungs showed marked fatty embolism; brain not examined; œdema of lungs; marrow crushed.

The second case was a male, seventy-two years old, with fracture of the upper end of the humerus. On the following night he developed restlessness and delirium resembling delirium tremens, and died in collapse on the third day. Marked fatty embolism of lungs. Brain not examined.

Socin.[60]—Male, aged eighteen, with fracture of right femur, and complicated fracture of right tibia. Died on third day. Fat-embolism of lungs, brain, kidneys, and heart.

Prichard.[61]—Quoted by Graham as reporting an apparently authentic case.

Coats[62] also quoted by Graham as reporting an authentic case.

Wahncau.[63]—Girl, aged eight, fractures of both tibias, and infarction of fibula. Died on the third day. Fatty embolism of lungs, heart, and kidneys, and pulmonary œdema found at autopsy.

Bruns.[64]—Two cases from Bruns's clinic reported by Meeh, one a male, aged twenty-three, with multiple fractures of right humerus, fracture of radius, femur, and other bones. Died four hours after injury. Marked fatty embolism of lungs. The second case was a male, aged forty-two, with fractures of many bones. Died six hours after injury. Autopsy showed marked fatty embolism of lungs.

Warnstedt[65] describes briefly a fatal case of fatty embolism following extensive contusion of the subcutaneous panniculus, caused by an apparently slight injury.

Meeh[66] collected the cases of fracture in which the cause of death was ascribed to fatty embolism, 113 in all, including the 86 cases collected by Scriba. Of these he regards only fifteen as undoubtedly due to fatty embolism. These are the cases observed by Halm (four), one by Busch, one by Riedel, one by Schwenninger, one by Böttcher, one by Pinner, two by Zwicke, one by Socin, one by Wahncau, and the two from Bruns's clinic reported by himself. In only eleven of these cases was death ascribed to pulmonary fatty embolism alone. Only in four was cerebral fatty embolism observed, and in these cases there was a flooding of the entire circulatory system with fat. In eleven cases there was general or partial œdema of the lungs. In the two cases from Bruns's clinic, both of whom were fat people, there were numerous fractures with marked crushing of the soft parts; the lungs were full of fat, but none was found in the systemic circulation. Accordingly he does not accept Scriba's dictum that fatty embolism is fatal only when emboli are found in the brain. He concludes that fatty embolism is a very common complication of fractures, but in the great majority of cases is not dangerous. Only rarely does it terminate fatally, either as the result of extensive embolism of the lungs or brain, or of the combined action of the emboli on various organs and the consequent disturbance of their functions.

Barack[67] discussed the cause of death in fatty embolism, and observed that the most important point in the diagnosis of pulmonary or cerebral embolism is the length of time between the entrance of fat into the circulation and the death of the patient.

Colley[68] reported a case of fatal fat-embolism after brisement forcé without injury to the bones. He gives a detailed description of the gross and microscopic findings, and called especial attention to the changes in the heart muscle,—areas of fatty degeneration surrounding capillaries filled with fat-emboli. He includes a second case of brisement forcé in a girl, eighteen years old, showing late rhachitic changes and marked atrophy of the bones. Twenty days after the operation the patient developed paralysis of the right facial nerve and arm, the temperature rose to 40° C., deep coma set in, and three days later death ensued with symptoms of pulmonary œdema. Autopsy showed a small number of fatty emboli in the lungs. The most important feature of Colley's report is the focal fatty degeneration of the heart muscle. He reviews the literature imperfectly for similar observations, and criticises Scriba's dictum that in fatty embolism death is never due to cardiac disturbance. He quotes Busch's observation of fatty degeneration of the heart muscle in the first case of fatty embolism he described, the patient dying thirty-six hours after the injury. Busch attached no significance to this change, and from his protocol we can not be sure that there was no other cause for the degeneration. In his survey of the literature he found no especial stress laid on the cardiac changes in fatty embolism. No previous writer had demonstrated so clearly that fatty degeneration of the heart is the result of obstruction of the capillaries by fat-emboli.

Hirsch[69] reported a case of comminuted fracture of the tibia and fibula. On the third day the patient developed restlessness, dyspnœa, and subnormal temperature, and died apparently from collapse. Lungs showed fatty emboli.

Ribbert[70] reported human cases and results of animal experiments. Showed that simple concussion led to fatty embolism in animals.

Ferguson[71] observed a case of fatty embolism of the lungs in a woman twenty-two years of age, whose breast was freely incised for diffuse suppuration. A milky, oily fluid escaped. Following the operation there was marked dyspnœa and restlessness. The lungs only were examined, and these showed marked fatty embolism.

Finotti[72] reported a case in a young man, aged eighteen years, who, after jumping from a second-story window without apparent injury, died twenty-four hours later from marked fatty embolism. Bloody effusions mixed with fat were found in the left knee and in both ankle-joints. The talus in both ankle-joints was fractured, as was also the head of the left tibia.

Ahrens[73] collected the cases of fatal fatty embolism following brisement forcé, abstracting the cases reported by Wahncau, Colley, and Finotti. He mentions also a case of fatty embolism following resection of the knee, which was reported by *Vogt*,[74] and concludes that even the most cautious use of force may cause such damage to the bones that a fatal fat-embolism may result.

Pomatti[75] reports a single case of cerebral fatty embolism with countless miliary ecchymoses of the brain substance, following subcutaneous fracture of the tibia. He notes the occurrence of multiple fibrin-thrombi in the cerebral vessels, and necrotic changes in the tissue about the plugged-up cerebral vessels. Symptoms set in twelve hours after accident; death occurred on the third day. The symptoms were mental stupor, trismus, tonic convulsions of extremities, ascending temperature, and collapse.

De Groube[76] collected 211 cases from literature and reported one fatal case following fracture.

Lympius[77] reported the case of a female, aged seventy-one years, dying suddenly during chloroform narcosis while her knee was being straightened. Lungs showed fatty embolism. There was no fracture. Subcutaneous panniculus was thick, and the muscles showed marked fatty change.

Payr[78] reported the fifth case of fatty embolism following forcible stretching of the limb for contracture. Ether narcosis. On the next day the patient collapsed, became cyanotic, dyspnœic, and restless, although the mind was unclouded and the temperature normal. Autopsy showed fatty embolism with lymphatic status. Payr attempts to demonstrate that the relationship between the latter condition and death from fatty embolism explains the disproportion between the trauma and the fatal outcome.

In a second publication Payr (1899) distinguishes two kinds of fatty embolism, a respiratory and a cerebral form, and reports two more fatal cases of pulmonary fatty embolism associated with the status lymphaticus.

Jentzsch[79] added ten cases from literature to the fifteen positive cases of fatal fatty embolism following fractures collected by Meeh. He gives details of three more cases (one following brisement forcé) from among the two thousand fracture cases in Bramann's clinic; fever occurred in all three cases, and this he regarded as a ferment-fever due to the "resorption of fibrin-ferment."

Carrara[80] found fatty emboli in the lungs in twenty-eight cases out of 102 examined. In seventeen cases of fracture they were found in seventy-six per cent. It was found also in diseases of the lung and kidneys, in burns and scalds, and in phosphorus poisoning.

Eberth[81] compared two cases of fatal fatty embolism, one occurring in a healthy man, the other in an anæmic girl suffering from chronic rheumatism. In the first case numerous fatty emboli were found in the general circulation, in the second case only few, although the lungs were full of them. Eberth explains this as the result of the earlier disturbance of the circulation in the lung of the girl, the fat not permeating the altered lung as readily as the normal one.

Hämig[82] made a special study of fatty embolism of the brain from the clinical side rather than from the pathologic. Out of 377 male patients with fractures in the clinic at Zürich in the year 1898–99 there were five deaths for which the only cause that could be found was fatty embolism. All five showed also fat-embolism of the lungs, but the symptoms were those of cerebral disturbance. One of these (reported by *Krönlein* and *Weismann*[83]) was trephined as the result of a mistaken diagnosis of meningeal hemorrhage (compare below). Symptoms, such as increasing stupor, delirium or coma, rising temperature, etc., appeared within six to eight hours after the accident. Death took place within a day and a half to six days from the time of injury. In two cases fat-emboli were found in the lungs, heart, and brain; in two in the lungs, heart, brain, and kidneys; and in one in the lungs, heart, brain, kidneys, and spleen. There was œdema of the lung in four cases. Fat-emboli and hemorrhages with surrounding yellowish zone were found in the heart muscle, and Hämig thinks it possible that these had an influence in bringing about the fatal result. He selects from literature twelve cases which show the especial features of fat-embolism of the brain: one case each of Busch, Czerny, and Flournoy, three cases of Halm, one of Socin, three of Ribbert, one each of Pomatti and Colley. He refers also to a case regarded by *Demisch*[81] as a case of healed fatty embolism of the brain. A young man, twenty-three years of age, after a fracture of the thigh developed on the fifth day fever, stupor, and dyspnœa; on the next day apathy and paresis of extensors of fingers. Slow recovery.

In the brains of his own cases he found miliary hemorrhages and thromboses, and attributes the symptoms of cerebral disturbance to the production of these rather than to the mere presence of fatty emboli in the cerebral vessels. Since fat is found in the urine of many cases of fracture with few or no symptoms, and from the fact that if fat gets to the kidneys it must also reach the brain, it is evident that in these light cases there was no serious damage to the brain tissues.

The increase of temperature observed in his cases Hämig explains by the assumption of an irritation of the heat-centre, and suggests that Scriba's failure to observe fever in the animals experimented upon was due to the fact that, after the first twenty-four hours, no temperatures were taken. Hämig also advances the theory that the "delirium nervosum" seen rarely in cases of fracture is probably a secondary result of fat-embolism of the brain.

Engel[83] observed a case of fatty embolism in a tuberculous lung following rupture of the liver caused by a slight fall. Symptoms of cyanosis, dyspnœa, foamy expectoration, pulmonary œdema.

Brodbeck[84] reported three new cases of fatal fat-embolism following rédressement, fracture of the bone, and injury to soft tissues respectively. To these he adds a fourth case of pulmonary fatty embolism in a man who had been run over by a heavy wagon. As this case showed other fatal injuries he did not regard the fatty embolism as the cause of death.

Fuchsig.[85]—Case of a seventeen-year-old girl falling from third story. Fracture of leg. On the following day unconsciousness, tonic and clonic convulsions, rising temperature, fat-drops in the urine. Death 72 hours after trauma. Fat-emboli in lungs and brain. Large hemorrhage in corpus striatum. Open foramen ovale.

Preindlsberger[86] is quoted by Brenziger as reporting a case of fatty embolism following rédressement.

Westenhoeffer[87] describes two cases of "cadaveröser Fettembolie" due to postmortem changes caused by the *Bacillus aërogenes capsulatus.* Hüttemann confirmed this by two similar observations, but the views of these two writers that fatty embolism may be a postmortal process are not tenable.

Euphrat[89] reported a death from fatty embolism during narcosis for treatment of a fracture of the neck of the humerus. Autopsy showed extensive fatty embolism of lungs.

Joachim[88] and *Seegers*[90] each reported a single case of fatal fatty embolism with cerebral hemorrhages following fractures, without adding anything to our knowledge of the subject. Seegers produced fatty embolism of the cerebral vessels experimentally in animals without causing hemorrhages of the brain, and assumed, therefore, that some other factor is necessary than the mere plugging of the vessels.

Brenziger [91] reported two cases of traumatic lipæmia. One, a laborer, thirty-nine years old, fracture of both legs. Pulse small, sensorium clouded, restless, fever. Died on following day. Fatty emboli in lung. Second, a laborer, twenty-seven years old, fracture of tibia. Same symptoms. Died on third day. Emboli of fat in lungs, small fat-emboli in vessels at base of brain.

Rössle.[92]—Portovenous fat-embolism of liver in case of infarction of mesentery and small intestine. Fat-emboli and localized areas of fat-infiltration throughout liver. Necrosis of overloaded liver-cells. Free fat in bile-passages. Absorption of fat into liver-cells by way of " Sternzellen."

Davidson [103] reported a case of complicated fracture of both legs in a young man of twenty-five years, with death from fatty embolism. Autopsy showed extensive fatty embolism of lungs, brain, and kidneys. Because of the relative infrequency of emboli in the vessels of the liver and the peculiar fatty infiltration of the liver-cells, Davidson concludes that the liver-cells removed a large part of the fat from the circulation.

Aberle [105] reported a number of cases of fatty embolism following orthopædic operations. The diagnosis was not always confirmed by autopsy. In one fatal case, in a child six years old with congenital club-feet, the operation of resection and rédressement was performed with normal narcosis, but cyanosis suddenly developed, and the child died six hours after the operation without recovering consciousness, in spite of the most extreme measures. Autopsy showed extensive pulmonary fat-embolism.

Riener [106] advises the insertion of a cannula into the saphenous vein, pushing it into the femoral as far as possible. When the constricting band around the limb is removed, the rush of blood through the cannula will wash out any fat that may be there.

Eichhorn [107] reported a fatal case of extensive fatty embolism of lungs, heart, and kidneys in a man seventy-one years of age, after a severe concussion of the skeleton without fractures.

Frischmuth [109] reported three cases of fatal fat-embolism from the surgical clinic at Königsberg, two of which were confirmed by autopsy. He repeated Ribbert's experiments on rabbits, and confirmed his findings that simple concussion is sufficient to produce fat-emboli in the lungs, and that crushing of the spongiosa without concussion causes fat resorption. In common with Lexer, he advises the use of a saw instead of a chisel in operations upon the spongiosa.

Wilms [111] reported a case of falling from the second story. Sixteen to twenty hours later the patient became soporific, the temperature rose to 39° C., respirations to 40. No fractures. Believing the cause to be fatty embolism with absorption of fat through the lymphatics, Wilms opened and drained the thoracic duct, large drops of fat appearing in the lymph. The patient recovered gradually, the fistula closing on the ninth day.

Von Lesser [112] carried out experiments with reference to the therapeutics of fatty embolism. Salt solution was injected directly into the right ventricle to revive the heart's action after air or fat had been injected into the jugular.

Bergemann[113] ascribes fat-embolism to the forcing of fat into the veins by the crushing of bones. He discountenances bone crushing in surgical operations, and also explains the occurrence of fat-embolism after rédressement without fracture as the result of direct pressure upon the atrophic ends of bones, which in turn forces fat into the veins. He believes that the lymphatics may take up some fat, but not enough to cause severe fatty embolism.

Fuchs[114] reported two cases of fatal fatty embolism; in one there was concussion without fractures; in the second fracture of the skull and rupture of the spleen. He mentions also a fatal case of fatty embolism in a young girl subjected to brisement forcé under chloroform anæsthesia. The clinical diagnosis in this case was chloroform poisoning; the autopsy showed marked fatty embolism. He believes that cases of fatal fatty embolism as the result of severe injuries without fracture of bones are not rare. He reports also the finding of fat in the lungs of eclamptics, in cases of delirium tremens, after resection of the intestine, after amputation of the mamma, etc., but in all of these the amount of fat was small.

Bürger[115] discusses the medicolegal significance of fatty embolism as a cause of illness and death, and emphasizes the fact that fatty embolism is a vital phenomenon.

Fuchsig[116] reviews the literature. He experimented with frogs, rabbits, and cats, using injections of pure olive oil and emulsions of the same. He concluded that the effects of intravenous and intra-arterial injections of oil depend upon the amount of the oil used and the rapidity of the injection. Death occurs only after injections of 2 Cc. to every 1000 Gm. of body-weight. The death may be pulmonary, cardiac, or cerebral; the pulmonary form is most common. When the intravascular pressure is sufficient to overcome friction, the oil passes the capillaries.

Schanz[117] reported ten cases of orthopædic operations on bones followed by signs of fatty embolism, the cerebral vessels evidently being clogged by fat from bone-marrow. One case was fatal; in another there was hemiplegia lasting some weeks. All of the others recovered after routine saline infusions, the salt solution being injected at several points to accomplish most quickly the desired dilatation and flushing of the capillaries.

Benestad[118] reported three cases of recovery from fatty embolism with multiple punctate hemorrhages in the skin. All were young workmen with fractures of the bones of the legs. After the injury they showed great restlessness, with gradually developing apathy, stupor, and dyspnœa; there was no cyanosis, but a weak pulse, pain in the lungs and severe cough, sputum like that of pneumonia. All recovered by the end of the second week.

Pacinotti[119] reported fatty embolism following severe burns of the skin, and holds that the hemorrhages so frequently seen after burns of the skin are due to fatty embolism and the resulting injury to the blood.

Fritzche[120] made an experimental study of fat-embolism in rabbits and dogs. He concludes that cutting of the bones may lead to fatty embolism, the veins taking up particles of fat. The mere concussion of the bones is sufficient to cause fatty embolism by the lymphatic route, the lymphatics taking up the fat and passing it into the circulation. In the latter case drainage of the thoracic duct may ward off danger, if this operation is performed when the symptoms of traumatic lipæmia first appear.

Godlee and Williams[121] observed two cases of fracture of the thigh, one a simple fracture, the other with some crushing of the bones. Within twelve hours both were comatose without noticeable pulmonary symptoms, the temperature rose rapidly, the pulse was low and rapid. Both died. No signs but those of fatty embolism, and no localizing lesions in brain. Superficial resemblance to compression of the brain, but without the pulse of compression.

Gröndahl[122] makes the most complete study of fatty embolism since Scriba's paper, critically reviewing the literature, and adding nine new cases (five of these cerebral fatty embolism with fatal termination and but three autopsies, three cases with cerebral symptoms but recovering, and one fatal case with pulmonary symptoms). In addition he reports on the investigation of the occurrence of fat-embolism in 108 cases of death from other causes, and describes a series of animal experiments. He compares the findings recorded in literature with his own, and gives a complete *résumé* of the etiology, symptomatology, and pathology of fatty embolism, without the addition of anything new. He emphasizes the importance of the process, the need for differential diagnosis and treatment. He notes the occurrence of fever in contradiction to the commonly accepted statement of Scriba that there is no fever. He does not mention the presence of fat in the sputum as a diagnostic sign.

Ziemke[123] discusses the postmortal origin of fatty emboli.

Beitzke[124] reports a case of fatal fatty embolism caused by injury to the stump of a leg that had been amputated the year before. Three hours after the injury there were dyspnœa, weakness, copious sweating and nausea, coma, a temperature of 39° to 40° C., and pulse of 120; death occurred on the following day. Autopsy showed no fracture, but fatty embolism caused by concussion. He believes that patients with bone injuries should not be subjected to transportation, massage, or tight bandages, and thinks that Wilms's method may be tried as a last resource.

AMERICAN CASES.—Few cases of fatty embolism have been reported by American writers, and American literature contains but few allusions to the subject. The paucity of text-book discussions has already been mentioned. The great number of accidents occurring in this country with frequent injuries to the bones would indicate many cases of fatty embolism, and if such are observed and diagnosed it is strange that they are not reported. It is but just to infer that they are not recognized; and the deaths following fractures and amputations are probably often reported as the result of shock, "heart-failure," concussion, hemorrhage, pneumonia, sepsis, etc., when the real cause is fatty embolism. This has been the actual pathological experience of the writer, and must be true of medical practice in general.

Fitz[93] is the first American to report (1876) an undoubted case of fatty embolism in a case of Cabot's. The patient was a young laborer suffering from fracture of the upper third of the thigh, with extensive ecchymoses. A few days after the accident he became delirious, and died on the eighth day. His symptoms, in the main, were similar to those of shock. The lungs showed numerous fat-droplets; the brain was not examined.

Bailey,[94] in 1877, reported the case of a robust man, thirty-five years of age, having a punctured wound in the upper third of the left leg, but without fracture.

Eight days later he began to show nervous symptoms which could with difficulty be distinguished from those of acute alcoholism. Two days after he became delirious, with temperature ranging from 103° to 104° C. Beyond a slight cough there were no pulmonary signs; severe diarrhœa at the close. Death thirteen days after injury. Examination of lungs, liver, and kidneys showed capillaries filled with fat-droplets; this was regarded as the result of injury to superficial tissues. Pus, however, was found in the wound, and the case may have been one of septicæmia rather than embolism.

In 1878 Fitz reported a second case in a laborer who had been run over by a hand-car. The hip was dislocated, and there was extensive hemorrhage into the tissues of the thigh. No fracture was found. He died eleven hours after the accident with the symptoms of chill, cyanosis, dyspnœa, and heart-failure. The pulmonary vessels were found to be filled with fat-droplets.

In 1879 *Fenger* and *Salisbury*[95] reported the case of a woman, aged forty-five, who had fractured the upper part of the left femur in a fall. On the second day after, she had slight spasms, became comatose, face pale, lips slightly bluish. On the next day loud, coarse râles were heard all over the lungs. A clinical diagnosis of fatty embolism was made by Dr. Fenger. This was confirmed by autopsy, death having occurred on the third day. Multiple capillary fat-emboli of the lungs were found, and ecchymoses were present throughout the brain and beneath the pleura. No pus found in the fractures. In this article there is a reference to a case reported by Merriman in the *Medical Record*, 1879. This reference could not be verified, nor any trace of the report found.

In 1881 *Fitz*[93] also reports a case of lipæmia and diabetic coma in which the pulmonary vessels contained a small number of fat-emboli. He refers to the similar cases reported by Sanders, Hamilton, and Starr, but does not believe that the emboli in his case were sufficient to cause any symptoms. In the same journal *Cabot* reports a case of recovery from "traumatic coma" in a youth of twenty-four with comminuted fracture of left leg.

Starr,[96] in 1880, reported a case of diabetes with lipæmia and fat-embolism dying in coma. Fatty emboli were found in the lungs, kidneys, and liver.

Brown,[97] in the same year, reported the case of a boy, sixteen years old, dying of diabetes with marked symptoms of "air-hunger." On autopsy a white substance, thought to be fat, was found in the pulmonary artery. The diagnosis is very doubtful; it is probable that the white substance was only a lardaceous clot.

Claussen,[98] in 1881, reports a case of fracture of the thigh in a man aged twenty-five. On the fourth day he complained of headache and dizziness, the temperature rose to 101.5°, followed by delirium with rapid breathing. Death two days later. The autopsy showed fractures of pelvis and femur. Portions of the lung examined by Dr. Fenger showed marked fatty embolism. The brain was not examined.

In 1884 *Park*[99] reported two supposed cases, but without autopsy demonstration, and another case, a male, aged forty-one, with fractures of tibia and femur and extensive laceration of the soft parts, who became comatose after operation, and died twenty hours after. Autopsy showed free fat in the heart's blood, and fat-emboli in the pulmonary vessels. Of the two suspected cases, one is of especial interest as following an operation for cancer of the breast in a very fat woman. During the operation it was noted that the venous oozing was free, and that the fat-tissue "seemed to melt down." The patient became comatose after the operation, and died six and a half hours later. No autopsy obtained. While the diagnosis is doubtful, Park held that the case was most probably one of fatty embolism. This case is similar to one reported in the writer's series.

Bonine and *Belknap*,[100] in 1886, reported a case in a male, aged fifty, suffering from fracture of the right femur as the result of a fall. On the seventh day insomnia, nervousness, and general mental disturbance developed. Temperature range, 101° to 103°, delirium and cyanosis. Some diminished resonance over lungs. After ten days the man began to improve, and recovered slowly. Free fat-droplets were found in the urine, and this finding forms a basis for the diagnosis of fatty embolism. The description of the urinary findings does not, however, remove the case wholly beyond doubt.

Whitney,[101] in 1892, reported an observation on a male, aged sixty-two, with a fracture of the right femur. On the third day dyspnœa, restlessness, vomiting, and a temperature of 101.5° developed. Autopsy imperfect. Pulmonary capillaries were filled with a highly refracting substance thought to be fat.

Bard,[102] in 1894, reported a similar case of recovery from fatty embolism, but the diagnosis is not substantiated.

Graham,[104] in 1907, reported very fully the case of a male, aged eighteen, who had been struck by a sled. After the accident the patient could not even rise. Mental condition was good, and there was no evidence of cerebral injury. Contused wound over the crest of the tibia. Temperature 101°, pulse 90. Lower third of left leg fractured. On the next day temperature range 101.5° to 104°, and complained of malaise. Next day comatose, and died two days later. Temperature before death 105.5°, pulse 164, respirations 60. Autopsy showed pinpoint ecchymoses of skin, brain, thymus, heart, and lungs (subpleural). Yellowish areas throughout heart muscle. Microscopically, multiple fat-emboli were found in the capillaries and smaller arterioles of all the organs, but most abundantly in the heart, lungs, spleen, kidneys, pancreas, and brain. In the heart and brain perivascular hemorrhages and areas of degeneration were seen. Fatty degeneration of ganglion-cells, muscle-cells, and liver-cells was observed in the neighborhood of the fat-emboli.

Graham also performed a series of experiments in rabbits; he observed fatty degeneration of the diaphragm in fatal cases of fatty embolism, and concludes that these lesions may in part account for the respiratory disturbance always observed. He found that the line of demarcation between fatal and non-fatal amounts of fat is ill-defined, individual susceptibility appearing to vary widely. An amount of fat which would be fatal if suddenly injected into the blood stream produces no unfavorable symptoms if introduced in divided doses at intervals of several days, such fat being eliminated by the kidneys and by the phagocytic action of the leucocytes. He distinguishes two lesion complexes—a pulmonary due to extreme blocking of the pulmonary vessels with less marked involvement of those of the heart, and the second as the result of a widespread embolism of the entire circulatory system, the pulmonary lesion being overshadowed by lesions of the heart, kidneys, and cerebral nervous system. In the first class, death is from asphyxia, and follows closely upon the trauma or disease which led to the entrance of fat into the vessels. In the second class, it depends upon multiple cerebral emboli, associated with embolism and fatty degeneration of the heart. In these cases death takes place only after the lapse of three to eight days.

Graham gives a very good review of the literature with an analysis of the leading features of fatty embolism. He calls attention to the increase of temperature in his own and other reported cases in contradiction of Scriba's dictum that there is always a lowering of temperature in typical cases. He also calls attention to the occurrence of fatty degeneration of heart muscle as deserving especial consideration, although other authors, particularly Colley, have also insisted upon its importance. The persistence of the thymus gland in his case coincides with the views of Payr, Ahrens, and Colley that a status lymphaticus exists in cases of fatal fat-embolism following brisement forcé.

Neither Graham's case nor his experimental work contributes anything new to the pathology of fatty embolism, unless it be the observation on the fatty changes in the muscle-fibres of the diaphragm. Scriba, however, reported the finding of fatty emboli and capillary apoplexies in the skeletal muscles. Graham found none in the latter.

Carrington,[106] according to the quotation given by Le Conte and Stewart, collected 276 cases of fatty embolism, only forty of which were confirmed by proper autopsy—the only other writer to mention the presence of fat in the sputum as a diagnostic sign, which he found in six cases.

McCracken [110] writes a paper, general in character, emphasizing the importance of fatty embolism after comminuted fractures and on the operating table, but says it is probably exceedingly rare. No new cases.

Field [126] reports a case of fat-embolism appearing in a patient suffering from chronic osteomyelitis after a ride of fourteen miles over a rough road. The patient developed cyanosis, dyspnœa, cardiac weakness, and coma, with fat in the urine. Recovery was slow, with intermittent attacks of dyspnœa and lipuria. Final result not known, as patient was lost sight of.

Other articles in American surgical text-books or systems are poor, and report nothing new since Scriba's paper. There seems to be a general failure among American surgical writers to recognize the importance of fatty embolism.

In addition to the cases collected from the literature, as given in the above historical survey, the following thirteen cases from my own pathologic laboratory are given in condensed form, as follows:

1. Case of fracture.
2. Amputation.
3. Concussion and fractures.
4. Injury to fat-tissues.
5. Fractures.
6. Injury to fat-tissues.
7. Fractures and concussion.
8. Fractures and concussion.
9. Fractures.
10. Fractures.
11. Concussion.
12. Injury to fat-tissues. Portogenous. Not fatal.
13. Extensive burns of skin.

Following are the condensed protocols of these cases:

ORIGINAL CASES

Case I.—Man of forty-five years, fracture of left femur. On the third day developed mental disturbances, dyspnœa, fever, pulmonary œdema, and weak irregular heart. Fat-droplets in urine and *in sputum.* (Fig. 13.) Numerous phagocytes containing large droplets of fat found in sputum. Small amount of free fat in urine. Became comatose and died in twelve hours.

Condensed Protocol.—Cyanotic skin, marked hypostasis, foamy fluid from mouth. Marked pulmonary œdema, small hemorrhagic infarcts in lung. (Fig. 1.) Subendocardial ecchymoses. Large yellowish clot in right heart, made up largely of fat, extending into pulmonary artery. Right heart greatly dilated. Small bleeding points on cut surface of brain. Other organs show marked passive congestion. Microscopic examination showed numerous fatty emboli in lung with marked hemorrhage and œdema. Fat-emboli found in all organs. Small capillary apoplexies and areas of degeneration throughout brain. Areas of fatty degeneration in heart and liver, surrounding plugged capillaries.

Case II.—Male, age forty-five to fifty, amputation of femur. On third day developed severe dyspnœa and pulmonary œdema. Sensorium clear, but patient was very restless. Temperature 102°. Died in ten hours. Lather-like fluid running from mouth; contained fat-droplets and phagocytes containing fat-droplets. Urine not examined.

Autopsy Protocol (condensed).—Marked hypostasis and cyanosis. Right heart greatly dilated, and contained large, yellowish-mixed clot composed chiefly of fat. Pulmonary œdema and hemorrhage. Other organs showed marked passive congestion. Examination of stump revealed a large amount of fatty bloody fluid; no infection.

Microscopic examination showed extreme fatty embolism of lungs with much œdema and hemorrhage. Few emboli in other organs. Marked passive congestion. No thrombi or hemorrhages. Atrophy and beginning fatty degeneration of heart muscle.

Case III.—German, aged sixty years. Buggy struck by train. Thrown some distance, striking on head and shoulders. Unconscious when picked up. Remained so through night, dying next morning. Rectal temperature 104°. Clinical diagnosis: Concussion, intracranial hemorrhage, fracture of skull. Temperature before death subnormal.

AUTOPSY PROTOCOL NO. III

Body.—Well built, no anomalies on skeleton. Length 157 cm. Skin slightly pale, no œdema. Moderate hypostasis over back, and numerous ecchymoses and small cuts over surface of body, largest one over the right cheek. Right inguinal hernia over which the skin is pigmented. Musculature in good condition. Small amount panniculus. Rigor mortis present throughout. No broken bones.

Head.—On left side of vertex there is an incised scalp wound two inches in length, and smaller bruises over scalp. No depression can be felt in region of cut on head. There is a large ecchymosis in skullcap over vertex. The cut in the scalp extends through the periosteum, which is adherent, tissues about the cut infiltrated with blood. There is no subperiosteal hemorrhage, and no external fracture of the skullcap. There is an ecchymosis over lower part of left temporal. The dura is adherent anteriorly. The skullcap is 4 mm. thick, and is very thin over the pacchionian bodies, which are hypertrophic and dark-red in color. The lamina vitrea is dull and rough throughout. There is no fracture in the skullcap. The dura is thickened with about normal tension. The floor of the longitudinal sinus is filled with hypertrophic and deep-red pacchionian bodies, but contains no clots. There is a subdural extravasation on the right side about 1 inch by 1½ inches wide, the clot clinging to the dura. The dura is more adherent than normal along the longitudinal sinus. There is a large clot over the left half of the tentorium. The pial veins are greatly congested. Over the entire cortex, but most marked over the occipital lobe and the cerebellum, is extensive hemorrhage —the blood being chiefly in the subarachnoid space. Beneath the pia are found several fairly large-sized clots. Small areas of congestion are seen over the cortex, most marked over the left hemisphere near the longitudinal sinus. The carotids show a moderate atheroma, which is most decided upon the left side. The circle of Willis also is slightly atheromatous. The anterior and posterior horns of the left lateral ventricle are filled with fluid blood, and the same is true of the right ventricle. All the vessels of the brain are enormously congested. The cut surface of the cerebrum and cerebellum shows an increased number of bleeding points, but there are no hemorrhagic areas in the cortex, nor is there any hemorrhage into the basal ganglion or internal capsule. The hemorrhage seems to be entirely meningeal. There is a bloody exudate in the base of the skull which contains small clots.

Thorax.—Muscles dark brownish-red, rather dry, do not tear easily. The eighth rib is slightly ossified. The diaphragm on the right is at the fourth intercostal space, on the left at the fifth intercostal space. No fluid found in the pleural cavity, and no remains of thymus. The lungs are very voluminous, covering up the heart. The sternum and mediastinal tissues are negative. Apex of heart is inside the nipple line in normal position. The pericardial sac is not distended, and contains a normal amount of clear fluid.

The *heart* is smaller than the cadaver's right fist, and weighs 340 Gm. There is a large soldier's spot over anterior wall of right ventricle. The pericardium is smooth and shiny. The right heart is collapsed and empty, the left heart full. The left ventricle contains fluid blood only; the mitral orifice barely admits two fingers and its flaps are thickened; wall measures at its thickest point 20 mm. The aortic opening admits the thumb with ease, though the flaps are slightly curled and show some calcification. The right heart is empty, and the wall of the ventricle measures 5 mm. at its thickest part. The tricuspid orifice barely admits three fingers, and the flaps are thickened. The pulmonary valves are negative. The heart muscle is brownish-red and of normal consistency. Aorta shows slight diffuse arteriosclerosis.

Lungs.—The left lung is adherent throughout, the adhesions being easily torn; the right lung also is adherent, the adhesions being mostly tender and easily torn, but stronger over the base. The left lung is voluminous, the edges emphysematous. The visceral pleura is covered with old adhesions, especially over the base. The lung is pinkish-gray in color, with slight hypostasis and moderate anthracosis. The cut surface yields an abundant exudate filled with air bubbles. The bronchial glands are heavily pigmented, and one contains a calcified tubercle. The larger bronchi are filled with clear, foamy exudate containing fat. The larger vessels are negative. The right lung is very voluminous, and the visceral pleura is covered with old adhesions, which are most marked over base. The cut surface presents same appearance as the left. The large bronchi are completely filled with foamy exudate containing fat. The large vessels are negative, and the bronchial glands show the same pigmentation. In the small vessels free fat is found.

Abdomen.—No fluid in the peritoneal cavity. The sigmoid flexure is distended with gas, and lies in the median line between the umbilicus and the pubis. The amount of omental fat is small.

The spleen is of normal size and triangular in shape. Over the anterior surface the capsule is markedly thickened and hyaline-like, and is considerably thickened over the whole spleen. The pulp is dark brownish-red and bleeds feebly, the trabeculæ are increased, the follicles atrophic.

The ureters are negative; the bladder contains a quantity of clear yellow urine, and the walls are thickened.

The duodenum is negative, also the bile-passages.

The stomach is dilated and contains partly-digested food. Postmortem digestion has already begun. The small intestines are negative, and the appendix normal. The large intestine and rectum are negative. About two inches of small intestine are in right hernial sac, and easily removed. The liver is atrophic but swollen; it is soft, and its capsule stretches and tears easily. The cut surface is yellow in color and presents a fatty shine, is moderately rich in blood. There is a cavernous angioma in the right lobe. Liver lobules do not show distinctly. The gall-bladder is enlarged and full of bile. The mesenteric glands are slightly enlarged, and two of them hemorrhagic. The tunics of the testicles are thickened, and there is a double hydrocele.

MICROSCOPIC FINDINGS

Fatty emboli in capillaries of lung only. Passive congestion of all organs. Marked œdema of lungs.

Case regarded as one of fatty embolism due to violent concussion of all the bones.

CASE IV.—Female, aged forty-nine, cancer of breast. Removal of gland with minute dissection of axilla. Patient very fat. Adipose tissue very soft and crumbling. Seemed to "melt away." Contained numerous bleeding veins. Oil-droplets in great numbers ran from wound. Twelve hours after operation became delirious and comatose. Very rapid and feeble heart. Signs of marked pulmonary œdema. Foamy fluid containing fat-droplets ran from mouth. In urine drawn by catheter without lubricant numerous fat-droplets were found. Died on the next day. Autopsy refused. Clinical diagnosis of fatty embolism borne out by fat-droplets in urine and sputum. At death the wound contained half a pint of slightly blood-stained oil. Temperature before death rose to 101°.

CASE V.—Mr. W., a farmer, about forty years old. The bones of the left leg were shattered by the premature explosion of a blast. He did well at first, then became restless and apathetic, at times falling into a stupor, and had attacks of dyspnœa with marked fall of arterial pressure. His temperature ranged from 101° to 103°; his skin was pale, sometimes cyanotic; the sensorium dull and reflex excitability diminished. When dyspnœic there was a flow of foamy mucus from the mouth. The wound showed no sign of being infected, but the clinical diagnosis was sepsis. Amputation of the leg was decided upon, and was performed at the middle of the thigh. The patient almost immediately fell into profound collapse with high temperature, dyspnœa, signs of pulmonary œdema, low arterial pressure, Cheyne-Stokes respiration, and coma, and died the next day, three weeks after the accident.

AUTOPSY PROTOCOL

General External Examination.—Body well nourished, with good supply of fat and well-developed muscles. The skin was in fair condition; there was no œdema and but moderate hypostasis over back. The right thigh had been amputated at about the middle, the stump was covered with surgical dressings, and was not examined. The upper extremities showed slight rigor mortis. There was no body heat.

INTERNAL EXAMINATION.—*Head.*—No scar or depression was seen in periosteum or skullcap. The pacchionian bodies were unusually large. Examination of meninges was negative, as were also base and interior of brain, with exception of numerous pin-point hemorrhages. The spinal cord was not examined. The dura was negative.

On section the muscles were dark red, dry, and easily torn. There was no fluid in the abdominal cavity, and the position of the abdominal organs was normal. The diaphragm extended on right side to the fourth intercostal space, and on the left to the fourth rib.

Thorax.—There were fresh adhesions on right side of thorax which were easily detached, especially over the base, and old adhesions over the left apex, with only slight adhesions over the rest. No fluid was found on right side in pleural sac. The left lung showed an area of bronchopneumonia near base in lower lobe. The right lung was firmly adherent over base, and showed hypostatic congestion and a few areas of bronchopneumonia, but less marked than on left side. There was marked œdema in both lungs, and quite marked hypostatic congestion. Fat-droplets were found in the sputum and in the pulmonary alveoli. The small arteries were filled with plugs of fat.

Heart.—Weight, 13 ounces. Pericardial fluid was only slightly increased and clear. White clots in the right auricle were very yellow and contained free fat. A mixed clot in the beginning of the pulmonary artery contained free fat. The heart muscle was a little brown and very firm. Valves were normal. The aortic valve showed slight thickening, as did the endocardium of the wall of the left ventricle. The heart was slightly hypertrophied.

Spleen.—Weight, 8¼ ounces. Enlarged, rather soft and dark, stroma increased, and showed a few unusually firm areas.

Left Kidney.—Weight, 5¾ ounces. Capsule was thick and adherent. Old cyst found under capsule. Cortex was atrophied, connective tissue increased, and kidney rather firm. There was slight degeneration, cloudy swelling, and fatty change.

Right Kidney.—Weight, 5½ ounces. The capsules were thickened and adherent, the cortex atrophied, and the kidney firm, showing cloudy swelling and fatty degeneration.

Adrenals.—Showed usual postmortem change.

Liver.—Weight, 4 pounds 4 ounces. Showed fatty degeneration and cloudy swelling. The central zone was pale; the lobules were distinct with fatty change in periphery. The liver was soft and flabby, tore easily, and had a cloudy, cooked appearance.

Pancreas.—Was grayish-yellow and unusually soft.

Intestines, stomach, retroperitoneal glands, and blood-vessels were negative.

The external genitals were negative. The bladder was slightly thickened, and the prostate much enlarged. The testicles were negative.

Microscopical Findings.—Fatty emboli in capillaries of lungs, kidneys, and brain; capillary hemorrhages in brain; œdema, hemorrhage, and bronchopneumonia of lungs; fatty degeneration and brown atrophy of heart; atrophy and fatty degeneration of liver. (Figs. 2, 8, and 10.)

Case VI.—Woman, aged eighteen, delivered of twins at term, developed symptoms resembling eclampsia. Died three days after delivery. Symptoms were coma, convulsions, pulmonary œdema, and cardiac insufficiency. Temperature 104° to 105°, respirations 60, pulse 150, almost imperceptible.

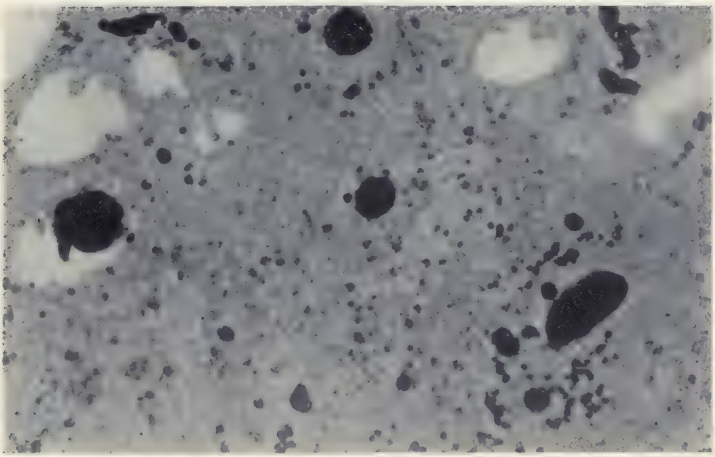
Condensed Protocol.—Heart dilated, chicken-fat clots in right auricle and ventricle. Sub-epicardial and endocardial hemorrhages. Punctate hemorrhages and areas of fatty degeneration in heart muscle. Marked œdema, congestion, hemorrhagic infarction, and bronchopneumonia of lungs. Thyroid much enlarged; contained no colloid. Numerous bleeding points in cortex. Marked parenchymatous degeneration in kidney and liver.

Microscopic Examination showed the presence of *fat-emboli,* numerous placental cells, and bone-marrow giant-cells in lungs. Extreme œdema, congestion, hemorrhage, and bronchopneumonia. No fat-emboli found in any other organ, but brain showed numerous capillary hemorrhages and areas of beginning degeneration. Similar areas were found in the heart muscle. Kidneys and liver showed extreme cloudy swelling and fatty degeneration. Marked congestion of all organs.

Case VII.—Male, tramp, age unknown, about forty, struck by train and thrown some distance. Fracture of left humerus and left femur, numerous contusions and lacerations. Was unconscious when brought to hospital. Died on the second day without recovering senses. Cheyne-Stokes phenomenon. Heart rapid, very weak. Low arterial pressure.

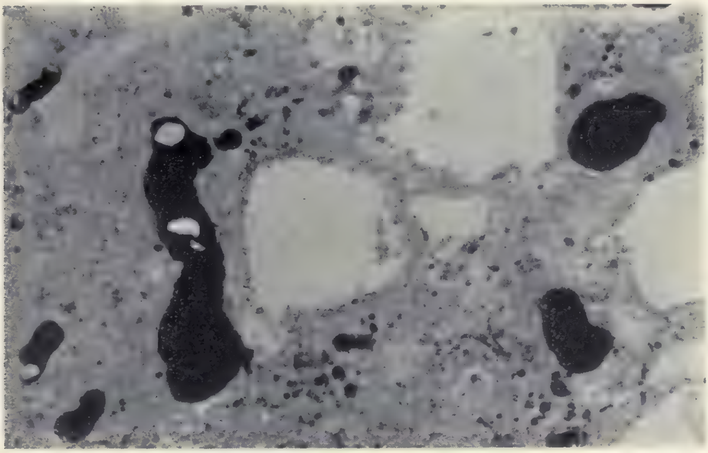
Autopsy Protocol (condensed).—Body very dirty, covered with lice. Vagabond's skin. Obscene tattoo marks on arms. Numerous cuts and bruises. Heart dilated, right side filled with large, yellowish chicken-fat clot containing free fat. Free fat-droplets in pulmonary vessels. Subendocardial punctate hemorrhages. Lungs showed marked œdema, congestion, and hemorrhages. Punctate hemorrhages in brain. Cloudy swelling and fatty degeneration of kidneys and liver. All other organs markedly congested. Focal areas of fatty change in heart muscle. Urine in the bladder covered with layer of oil.

Fig. 1.



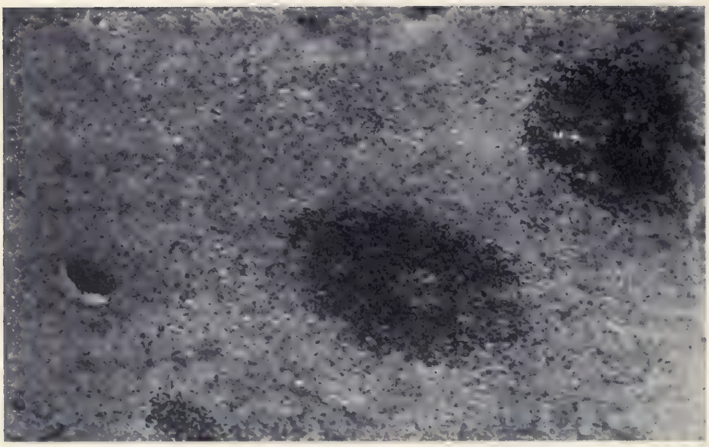
Lung from case of fracture of femur. Death three days after injury. Osmic acid fixation. Unstained.

Fig. 2.



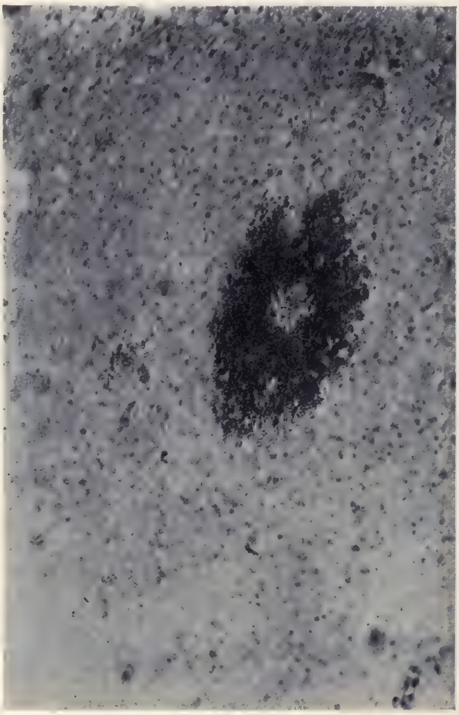
Lung from case of fracture of tibia. Death three weeks after injury. Osmic acid fixation. Unstained.

Fig. 3.



Multiple capillary hemorrhages in brain, due to fatty embolism. Fracture of both legs. Death ten hours after injury. Symptoms suggested large meningeal hemorrhage. Patient trephined. No hemorrhage found. Formalin fixation. Hæmatoxylin and eosin stain.

Fig. 4.



Small perivascular hemorrhage from brain of same case as in Fig. 3. Low power.

Microscopic Examination.—Extensive fatty embolism of lungs, brain, heart, kidneys, liver, and all other organs. Areas of fatty degeneration about plugged-up capillaries. Minute hemorrhagic infarctions with beginning necroses in heart, brain, and striped muscles.

CASE VIII.—German, about forty-five years of age, mason, fell about thirty feet. Frontal and facial bones showed multiple fractures. Numerous large flesh-wounds. Multiple fractures of extremities and vertebral column. Became comatose shortly after the fall, and died about ten hours after. Clinical diagnosis, meningeal hemorrhage.

Protocol (condensed).—Multiple comminuted fractures of facial and frontal bones. Fracture-dislocation of spine at level of seventh and eighth dorsal vertebræ. Subperiosteal hemorrhage over frontal region. Meningeal hemorrhage. Large masses of yellow, fat-like cruor in right auricle. Œdema of lungs, which also showed small, rounded hemorrhagic areas. Large hemorrhage in posterior mediastinum. Microscopic examination showed numerous fat-emboli in lungs, with marked œdema, congestion, and hemorrhage. No emboli found in other organs. Yellow clot in heart composed chiefly of fat.

CASE IX.—M. A., male, age sixty-six, markedly senile. Slipped on icy pavement and fell, fracturing left femur—a comminuted fracture. Shortly after accident he became dyspnœic and cyanotic. Foamy, lather-like fluid ran in a constant stream from his mouth, and was occasionally blood-stained. He showed marked symptoms of shock, gradually became comatose, and died on the third day after the accident. Free fat-droplets in great numbers were found in the sputum, also numerous phagocytes containing great numbers of fat-granules. Urine showed no fat. Temperature, 102° to 103°. Clinical diagnosis was pneumonia following fracture of femur.

AUTOPSY PROTOCOL

General External Examination.—The body was 170 cm. long, and was large with large chest. The epigastric angle was wide, the abdomen distended below the umbilicus. The left leg was rotated outward and shortened, the thigh swollen and œdematous. There was distinct crepitus, the upper fragment overriding the lower. Section of thigh showed fracture of shaft just below trochanter, also two smaller fragments, and about 500 Cc. of semi-fluid, grayish emulsion of fat escaped from surrounding tissues. The skin was pigmented over arms; the hair fairly abundant, the beard abundant and gray; the musculature fair; the teeth absent in upper jaw, a few decayed ones below. No rigor mortis. Panniculus was moderate over abdomen—pale yellow on section. There were small, pultaceous masses in left, also small cyst; in fat of right side was small body resembling lymph-gland. The scrotum was œdematous. There was no body-heat. A greenish discoloration over the abdomen. The superficial veins were congested. The skin over the abdomen showed subcutaneous nodules, and there were small erosions over left side covered with scabs. The left thigh showed extravasation of blood.

INTERNAL EXAMINATION.—*Head.*—The scalp was negative, the periosteum negative except for thickening over parietal cones. The skullcap was removed only by cutting dura; in postparietal region was an area of depressed bone 15 mm. in diameter which was discolored and showed bleeding vessels. Outer table was eroded, probably from cephalhæmatoma at birth. Dura was adherent all over convexity. The longitudinal sinus contained soft, currant-jelly clots, white clot, and fluid blood; had odor of putrefaction. Basal sinuses contained currant-jelly clots and fluid blood. Inner meninges showed thickened adhesions between dura and arachnoid. Anterior cerebral artery showed sclerosis. Frontal lobes showed atrophy, congestion, and œdema. Lateral ventricles were dilated. Pineal gland was softened and disintegrated. The left vertebral artery was dilated, the basilar sclerosed. Weight of brain, 1400 grammes.

Thorax.—Diaphragm reached to fifth rib on right, same on left, and was arched downward on both sides. Apex of heart was behind sixth rib inside nipple line. Pleural cavities contained small amount of fluid. Pericardium was deeply stained with blood.

The *heart* was very large, soft, and flabby, and weighed 585 grammes. Both ventricles were dilated. Subepicardial fat was increased. Right auricle contained large agonal clot; was greatly dilated. Anterior wall of right ventricle showed soldier spot. Ventricle contained very large chicken-fat clot showing fat-droplets. Heart muscle was soft, tearing easily. Valves of the heart were negative, except that aorta showed beginning sclerosis. Heart measured 13 x 14 x 6 cm.

Left lung weighed 750 grammes, measured 26 x 19 x 5 cm. Was free except for small adhesions over lower lobe, which was rather voluminous and showed marked anthracosis. Border emphysematous. On section cut surface was moist. Pressure produced abundant cloudy exudate containing fine fat-droplets. There were elevated, slightly granular airless areas around small bronchi. Œdema was present. *Right lung* was free except for slight adhesions over lower lobe; similar in all respects to left. Weight 1170 grammes, measured 29 x 19 x 6 cm.

Fatty globules were found in lungs; frozen section stained with Sudan III showed marked fatty embolism.

The chicken-fat clot in right ventricle extended into pulmonary artery.

The smaller bronchi showed purulent exudate with distinct fat-droplets.

Aorta was dilated and showed arteriosclerosis and atheroma, with atheromatous patches in intima.

Trachea was of unusual size, congested, and filled with mucus containing fine fat-droplets.

Abdomen.—Abdominal cavity contained no fluid. Peritoneum was moist and shining. Omentum was moderately rich in fat, with congested veins. The lower border of the liver was low.

The *spleen* was very small and soft, with wrinkled and thickened capsule. On section the splenic pulp was atrophic, congested, and its stroma increased. Weight of spleen, 90 grammes; measurements, 10 x 7½ x 2 cm.

Left adrenal showed complete postmortem degeneration.

The *left kidney* showed retention cyst. On section was atrophic, the labyrinths swollen and cloudy, the blood-vessels congested. Weight, 230 grammes; measurements, 12½ x 6½ x 5½ cm. Cortex measured 3 to 4 mm.

The *right kidney* showed several retention cysts in cortex. The venæ stellatæ were engorged, the consistency diminished. Kidney had same appearance as left on section. The pelvis was dilated. The fatty capsule was abundant in both kidneys.

The folds of the *duodenum* were atrophic.

Pylorus was patent; admitted finger easily. There was a strong odor of H_2S in stomach. Mucosa of stomach showed complete postmortem digestion.

The *small intestine* was distended.

The *appendix* region was negative, appendix lying behind cæcum.

The *cæcum* was moderately distended, also colon.

The *liver* was three finger-breadths below ensiform in right nipple line, 2½ finger-breadths below nipple. Liver was soft, and showed cavernous hæmangioma. On section had appearance of nutmeg liver. Weight, 2120 grammes; measurements, 27 x 21 x 8 cm.

The *gall-bladder* was distended, and contained a number of small faceted gall-stones, chiefly cholesterin.

The *portal vein* was distended with thick, fluid blood.

The *pancreas* was atrophic, congested, and soft; showed postmortem digestion.

The *retroperitoneal lymph-glands* were atrophic, and vessels of this region were atheromatous.

Male Sexual Organs.—External examination of penis was negative. Scrotum was congested, macerated, and scaly. Tunics of right testis were thickened with increase of fluid between; the body atrophic. Left testis similar to right. Epididymis showed a number of cysts about the size of a pea. Prostate was about normal size; on section was negative.

MICROSCOPIC FINDINGS

Lung.—Frozen section stained with Sudan III shows marked fatty embolism of capillaries. Excessive sclerosis, healed tubercles, emphysema, œdema, congestion, a few areas of pneumonia. Free fat in sputum.

Liver.—Atrophy, chronic passive congestion, some fat-emboli, postmortem change, fatty infiltration.

Thyroid.—Marked atrophy.

Fat-emboli found in all organs; not so numerous as in lungs. Focal necroses and hemorrhages in brain and heart.

Pathological Diagnosis.—Bronchopneumonia, œdema, fatty embolism of all organs.

Case X.—B. R., motorman, age twenty-seven, both legs crushed in collision. Was removed to hospital and wounds dressed. He did not recover from anæsthetic; became restless, delirious; temperature was subnormal; showed loss of reflexes; coma increased with Cheyne-Stokes phenomenon. Heart was very feeble and rapid. Foamy fluid discharged abundantly from mouth, and was afterward found to contain free fat. There was no examination of urine for fat. After consultation surgeons trephined for meningeal hemorrhage, but no blood was found. Coma gradually deepened, temperature rose rapidly to 106°, and death took place about ten hours after the accident.

AUTOPSY PROTOCOL

General External Examination.—Body was 160 cm. long, well nourished. Skin was yellowish-white; greenish-blue over legs, with some dark spots. Teeth were good. Rigor mortis was marked; œdema in left leg; panniculus good. The conjunctivæ were clear. There was beginning hypostasis, and over the trunk were numerous petechiæ.

In right parietal region of head was a semicircular incision 8 cm. long with gashed edges. Within the hemisphere of this was another cut 2 cm. long. The cuts were closed with the exception of a drain in the larger which led directly to a trephine opening 4 cm. in diameter lying under the smaller gash. Through this opening protruded the brain substance,—soft, bloody, and suggesting pus. Edges of the wound were clean with exception of slight gray film.

There was a fresh abrasion, 2 x 4 cm., over right trochanter, and one over left, 1 x 2 cm. Legs were swollen. Left leg showed numerous abrasions. Crepitus was felt corresponding to abrasion over tibia. The leg could be bent at this point. Foot was normal but for dark-blue spots mentioned above. Right leg showed jagged wound over tibia on inside at junction of upper and middle third, 3 x 3 cm., through which bone protruded, and beneath skin anteriorly could be felt a splinter freely movable. Lower leg hung free; shortened as compared with the left. Over inner and outer aspects of right knee were large, superficial abrasions, outer 1 x 6 cm., inner 7 x 5 cm. On right side were two areas, one 4 x 2 cm., and light purplish, other 7 x 3 cm., similar in color but desquamated. Upper leg normal.

Head.—The scalp was thick and showed œdema about wounds. Six centimetres above left ear was another purplish spot corresponding with subperiosteal extravasation of blood. There had been bleeding under temporal muscle. Hemorrhage about wound extended back to occipital region. Firmly adherent posteriorly, the dura was otherwise free. Beneath dura the brain was covered with a hemorrhagic exudate. The longitudinal sinus was empty. Inner surface of dura away from opening was clear. Pia was slightly adherent over pacchionian bodies. Sinus at base of skull was free from hemorrhage. The membranes were torn away over wound, and brain substance bulged through opening. The pia was clear except for slight adhesions at base, and veins were congested. There was slight hyperæmia at base of brain. The vessels were free from sclerosis. The right hemisphere was lacerated, and showed hemorrhage through the area of laceration with softened tissues to a depth of 2 cm. This laceration involved upper part of second temporal and margin of first temporal convolutions. The convolutions were a little flattened. The white substance was covered throughout with many punctate hemorrhages. The brain substance was greatly congested, and there was diminished consistency of brain tissue.

The cerebellum showed similar hemorrhages in the white substance and some in the gray. The brain stem showed scattered punctate hemorrhages in left external capsule and in anterior part of interior capsule. Section through optic thalamus on each side showed two red areas, each 2 mm. across, with slightly depressed centres surrounded by margins in which the tissues were congested.

Thorax and Abdomen.—Diaphragm on right rose to level of fifth rib. Abdominal cavity contained no free fluid; intestines were moist. The mediastinum contained fat. There was no trace of thymus. The pericardium was smooth and contained about 25 Cc. of fluid.

Heart.—Measurements, 12 x 9 x 6 cm. Apex of heart was in mammary line. Heart was firm. The surface glistened over anterior part of right ventricle, to less extent over left ventricle, on which were small, bright-red pin-point spots. Everywhere over endocardium were bright-red spots. Scattered throughout myocardium were a few red points and numerous yellowish areas. Auricles were not dilated. The right ventricle contained some soft clot, the left a little fresh clot. The left ventricular wall was 4 cm. thick. Aortic valve was competent to water test; the flaps were thin. The mitral valve was not thickened, and its orifice was 1 cm. in circumference. The pulmonary valve was delicate, but otherwise negative.

Lungs.—Left lung sunk back evenly on opening thorax, and showed no adhesions. There were large reddish areas, and several black irregular pigmentations. The lung crepitated everywhere. The mucous membrane was smooth, pinkish-white. Bronchi showed frothy fluid containing fat-droplets. Veins contained fresh clot of blood, and arteries a little fluid blood. Lung on section was pink, and filled with frothy pink fluid. Right lung was voluminous with moist, dark-red surface mottled with bright-red, small superficial areas 2 to 4 mm. in diameter; some larger ones on posterior surface of lower lobe. The veins were empty; the arteries contained little fluid blood. The lung substance crepitated everywhere except in lower lobe, and on section was full of frothy fluid. The bronchi were filled with frothy, bright, bloody fluid. The mucous membrane was smooth and pinkish-white. The bronchial glands were swollen and red.

Mouth and Neck.—The tongue was smooth, gray-white, and dry. Tissues back of tongue were hyperplastic. Tonsils were large, showing irregular clefts, and were gray on section. Left tonsil contained several small cysts holding pus-like fluid. Larynx was smooth, and empty except for slight mucus. Trachea was empty, the mucosa showing some smooth superficial red spots. Œsophagus was negative. Thyroid measured 4 x 3 x 2 cm.; its cut surface was pinkish-red, and showed no colloid.

Abdomen.—Peritoneum was glistening; no pin-point areas above described.

Spleen.—Measured 12 x 7½ x 3½ cm., weighed 125 grammes. Spleen was large, dark purple, free, and smooth, with a few raised whitish areas suggesting connective tissue. The cut surface was smooth, moist, bright red, and trabeculæ distinct.

Adrenals.—Left measured 6 x 2 x 5 cm., weighed 8 grammes. Medullary substance was easily distinguishable, pale, firm. Right measured 5½ x 3½ x ½ cm., weighed 10 grammes; was firm, like left.

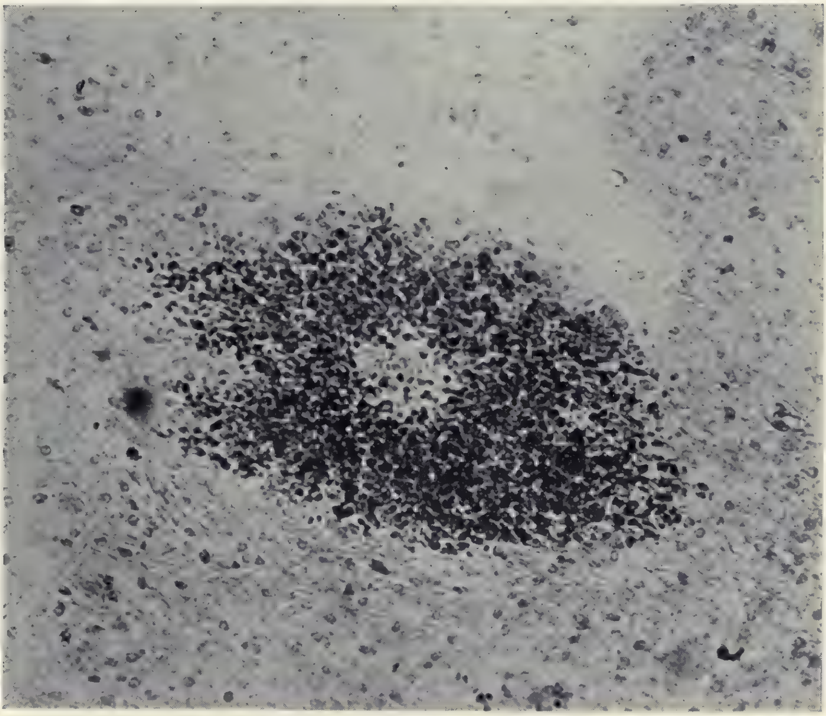
Kidneys.—Left measured 11 x 4½ x 4½ cm., weighed 140 grammes; was surrounded by a moderate amount of fat. Capsule stripped easily. Venæ stellatæ were moderately congested. Cortex was pale, 5 mm. thick, vessels here and there being injected. Right measured 10½ x 5¾ x 4 cm., weighed 138 grammes; was similar to left. In left side of pelvis near sacrum in retroperitoneal tissue was a dark-red area of diffused hemorrhage into mucosa.

Bladder.—Was distended with 800 Cc. of straw-colored urine. The wall was flaccid and grayish-white, with here and there red pin-point ecchymoses.

Stomach.—Duodenum was empty. Stomach contained about 500 Cc. of grayish-brown fluid. The walls were smooth and not swollen, the mucosa was normal, and the submucous vessels could be seen.

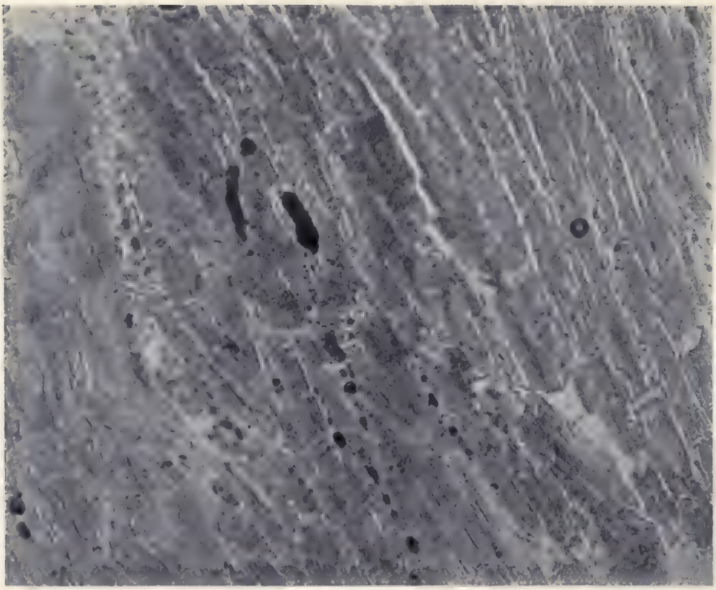
Small Intestine.—Was collapsed, jejunum was empty except for a little light-

Fig. 5.



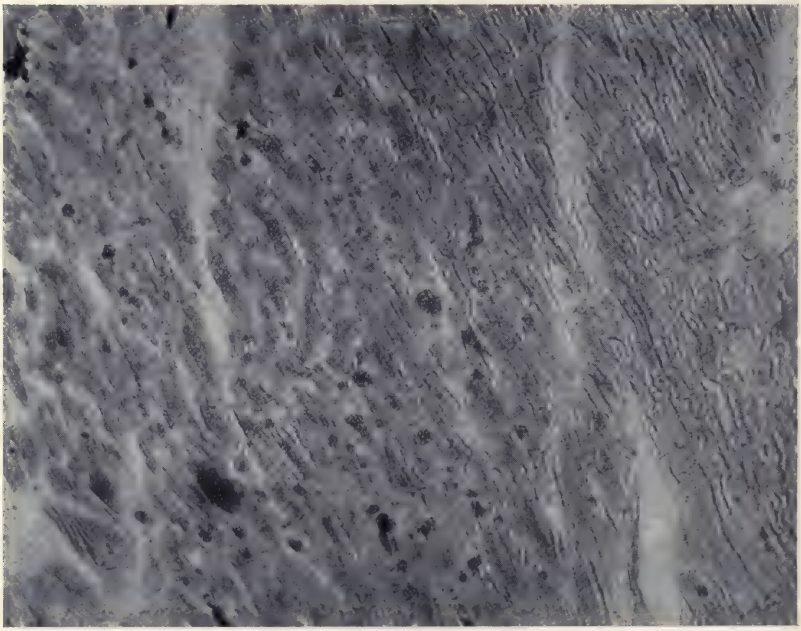
High-power view of same perivascular hemorrhage in brain as in Fig. 4. Area of central necrosis. Small anæmic infarct with hemorrhagic zone.

Fig. 6.



Small infarct in heart-wall due to fatty emboli, showing fatty degeneration of muscle of anæmic area. The injured heart-muscle takes up the fat from the plugged-up capillaries. Small hemorrhage in and about these areas of fatty degeneration. From case of fracture of both legs, patient dying ten hours after injury.

Fig. 7.



Photograph of area of fatty degeneration and fatty embolism from heart-wall of same case as in Fig. 6. Sudan III and hæmatoxylin stain of frozen section.

brown fluid. The mucosa was pale and smooth. In the mesentery, 300 cm. below duodenum and between folds at insertion to intestine, were a number of clear yellowish, translucent cysts.

Large Intestine.—Was smooth and injected, and contained little mucus; otherwise negative.

Appendix pointed to right anteriorly and was 10 cm. long.

Liver.—Weight, 1550 grammes. Was not enlarged; surface was injected, bright red, smooth, and glistening. Cut surface was pale and regular. The bile-passages contained bile. A small quantity of blood oozed from cut vessels. Here and there on cut surface were light yellowish areas, irregular in outline, glistening and raised, 3 x 4 cm. Liver structure within these areas was blurred, suggesting beginning fatty degeneration.

Gall-bladder contained about 40 Cc. of dark-brown bile; otherwise negative. *Portal vein* contained much fluid blood.

Pancreas was 15 cm. long, firm, with grayish-pink substance. Between pancreas and abdominal vessels was an extravasation 4 x 5 cm.

Retroperitoneal lymph-glands were not enlarged.

Aorta was smooth, elastic everywhere, and contained small amount of fluid blood. The walls were delicate. Vena cava was nearly empty.

Male Pelvis.—Right testis was small and soft, cut surface pink and moist; left was very small, similar to right. Tubules were easily seen and regular. The prostate was not enlarged, and the cut surface was smooth.

Abdominal muscles dark red on section. On section muscles of right lower leg are found suffused with blood; upper fragment of tibia projects through skin-wound. A movable fragment of bone, crescent-shaped, 2 cm. long, between upper and lower fragments of tibia. No signs of pus. Fibula broken at same level. Lower fragment passes upper posteriorly about 25 cm. Large effusion of blood through muscles of calf. Left fibula not broken. On cutting into muscles of calf similar large effusions are found. Fracture of tibia is V-shaped. No displacement.

Microscopical Findings.—Lung, fatty embolism, œdema, congestion, hemorrhage, pneumonia. Liver, cloudy swelling, fatty embolism, small localized areas of fatty degeneration and necrosis which are associated with larger areas of fat in the capillaries. Hæmatoidin in central zone. Kidney, fatty embolism, cloudy swelling, fatty degeneration. Brain, fatty embolism; surrounding the emboli are localized areas of hemorrhage, œdema, and fatty degeneration, these corresponding to small infarcts due to embolism. Many of these hemorrhages are large enough to be seen by the naked eye. The smaller arteries leading to these hemorrhagic areas are completely blocked with fat, as is shown by Sudan III stain. All organs show fatty embolism with local areas of fatty degeneration, cloudy swelling, simple necrosis, and hemorrhage corresponding to small infarcts due to embolism. This is beautifully shown in the heart muscle and striped muscle, as in the diaphragm, the adrenals, and other organs. In the striped muscles, particularly in the diaphragm, muscle-fibres nearest to the large fatty emboli show marked fatty degeneration. (Figs. 3, 4, 5, 6, 7, 9, 11, and 12.)

Case XI.—Male, aged forty, plasterer by trade. While intoxicated fell or was pushed down stairs. Broke both wrists and badly bruised head. Was taken to the hospital, where he did well for one week; then began to show mental disturbance. Temperature rose suddenly to 107°, was delirious, escaped from hospital in delirium, and was absent for two days. Marked dyspnœa, "air-hunger," and coma at the last. White foamy fluid like soap-lather ran constantly from mouth. Free fat-droplets in this. Sputum also contained numerous alveolar cells filled with fat-granules. Urine not examined for fat.

Autopsy by Coroner's Physician.—Imperfect. Lungs, liver, and stomach sent for examination. Fixed in formalin. On microscopic examination extensive fatty embolism of lungs. Few emboli found in liver, but the intralobular (central zone) fatty change gave evidence that the emboli had been dissolved out. Few fat-emboli in mucosa of stomach. *Coroner's diagnosis:* Acute alcoholism; fall not accountable for death. *Pathologic diagnosis:* General fatty embolism, result of fractures and fall; cerebral type predominating.

Case XII.—Boy, aged eighteen years, marked adipositas, infantilism, and general picture of tumor of hypophysis. Attempted removal of hypophyseal tumor in prolonged chloroform narcosis. Boy struggled violently. Died on following day. Autopsy. *Pathologic diagnosis:* Infantilism; adamantinoma of hypophysis (hypopituitarism); lymphatic constitution; persistent thymus; hyperplasia of thyroid and medulla of adrenals; general lipomatosis; postoperative cerebral hemorrhage; fatty embolism of liver alone. Liver showed marked central and localized fatty degeneration, with numerous large fatty emboli distending the capillaries in various portions of the liver-lobules. Endothelium and liver-cells in the immediate neighborhood showed marked fatty change.

Case XIII.—Miss R. M., aged eighteen, burned on both legs, thighs, back, and both arms; second-degree burns over two-thirds of body. Lived thirty-seven days. During this time showed intermittent attacks of stupor, air-hunger, lipuria, and pulmonary œdema with fat-containing sputum. Temperature very irregular, subnormal to 104°, usually 101° to 102°, pulse 100 to 140. Infusion of two per cent. sodium carbonate during one period of extreme dyspnœa relieved the air-hunger; further attempts not made. Pulmonary condition became more marked; appearances of bronchopneumonia. Autopsy showed a pulmonary fatty embolism, with a mould infection (aspergillus) of the bronchi, numerous hemorrhagic infarcts, hyaline thrombi, extreme congestion and œdema. Fatty embolism and pulmonary thrombosis followed by gangrenous bronchitis secondary to burns of skin regarded as cause of death.

EXPERIMENTAL

In spite of the fact that various writers have done a fairly large amount of experimental work with animals, a number of important points connected with fatty embolism need further elucidation. In the study of the human cases, the almost invariable presence of a dilated, paralyzed right heart containing large yellow, "chicken-fat" clots, made up chiefly of oil, led to a desire to see if the same condition could be produced experimentally.

Furthermore, the remarkable taking up of fat-droplets by the heart muscle, skeletal muscles, liver-cells, adrenal cells, splenic cells, etc., in the neighborhood of the emboli suggested an attempt to solve some of the problems connected with fatty degeneration and infiltration.

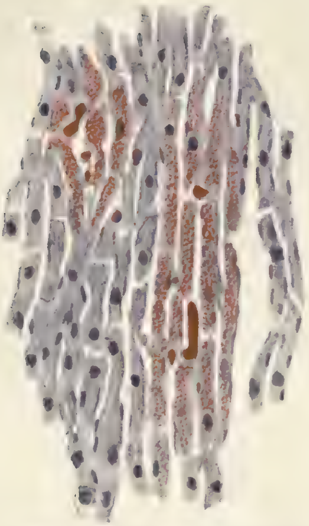
Rabbits, dogs, and chickens were used under the ordinary conditions of experimental work. Acid-free olive oil was employed in varying amounts; pure with one series of animals, and combined with Sudan III or Scharlach R. in another. The dye-oil was prepared in the same manner as that used in the experiments on regeneration or proliferation of epithelium.

Measured amounts of the oils were injected in different ways and into different vessels, according to the object desired. The tissues were either frozen directly and cut, or given a short preparatory fixation in four per cent. formaldehyde. When necessary, syrup or gelatin was used for imbedding before freezing. When the pure oil was injected the frozen sections were treated with osmic acid, Sudan III, or Scharlach R., counter-stained with hæmatoxylin, and mounted in glycerine.

A series of rabbits was first used to demonstrate the ordinary pathology of fatty embolism.

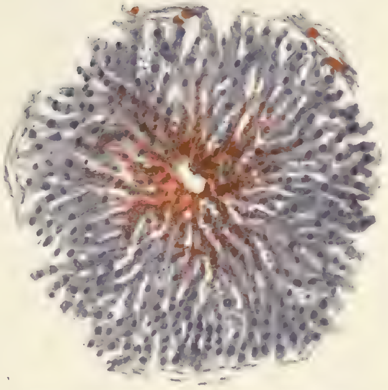
Experiments 1 to 6.—Six Belgian hares were injected with 4 Cc. of olive oil in the jugular. When injected rapidly this produces dyspnœa, muscular tremors, and slight convulsions leading to death in two to five minutes. Larger amounts cause death almost immediately. In these cases, on opening the dilated right heart, the ventricle and auricle contain soft friable masses of blood and fat-clot, usually filling up the ventricle and extending into the pulmonary artery. No matter how acute, fatty emboli are always present in great numbers in the lung, and occasionally in the organs of the systemic circulation. In the heart-wall itself a varying number of fat-emboli are found, but in these acute cases there is usually not much fatty degeneration. If the amount of oil is not too large, and

FIG. 8.



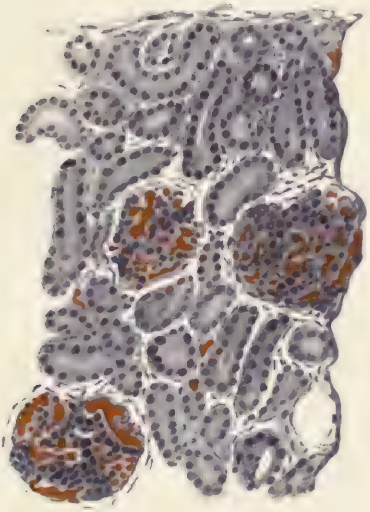
Infarcted area of heart-muscle showing fatty degeneration of muscle about fatty emboli, from case of fracture of tibia. Frozen section, stain Sudan III and hæmatoxylin.

FIG. 9.



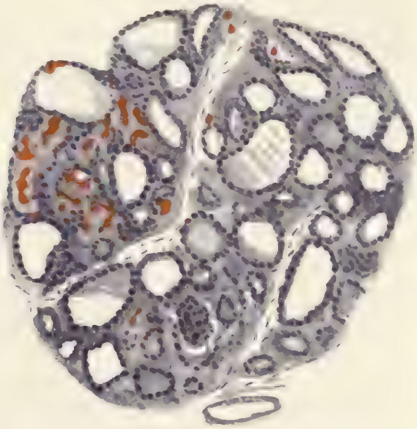
Section of liver from case of fatty embolism following fracture of both legs; death ten hours after injury. Fatty emboli in central zone of lobule. Surrounding liver-cells loaded with fat-droplets. Present appearances of fatty degeneration. Sudan III and hæmatoxylin stain, frozen section.

FIG. 10.



Section of kidney from case of fatty embolism following fracture of tibia. Free fat in urine. Glomeruli filled with fatty emboli. Free droplets in tubules. Sudan III and hæmatoxylin stain of frozen section.

FIG. 11.



Section of thyroid from case of fatty embolism dying ten hours after fracture of both legs. Thyroid was practically destitute of colloid. All capillaries filled with fatty emboli. Sudan III and hæmatoxylin stain, formalin fixation, frozen section.

if the animal lives for some hours, the muscle-fibres around the fat-emboli gradually lose their nuclei and stain a faint red with Sudan III or Scharlach R., while the fat-emboli in the area of focal degeneration are a deep homogeneous red. Similar areas are found in the skeletal muscles of animals treated for a longer time. With the one dose, fat-emboli may be found in any part of the body, although the lung shows the majority of them. Injections into the ear-vein give the same results.

The main features, that is, the common ones, of fatty embolism as we know it in man, can be reproduced in this way. Fat-droplets appear in the sputum, and also pass into the renal tubules.

Experiments 7 to 12 Inclusive.—Six Belgian hares were given injections of olive oil in divided doses of .2 Cc. at different intervals of time from three to twenty-one days. As Graham found, it is difficult to fix an arbitrary minimum fatal dose. The individual variations in animals, apparently of the same general characteristics, are very great. Our minimum dose we found to be larger than the 1 Cc. per 1100 Gm. of weight as roughly stated by Graham. Four or six grammes in divided doses frequently did not produce great disturbance or show a temporary dyspnœa, but our animals were larger than those used by Graham, weighing 2500 to 3500 Gm. or more. Our results with divided doses spread over a greater period of time agree with this, and, as he has pointed out, give microscopic pictures much more closely resembling those of human fatty embolism. Numerous emboli occurred in the lungs, pulmonary œdema and hemorrhage were seen; the heart, brain, cord, spleen, liver, kidneys, skeletal muscles,—in fact, all the organs and tissues,—showed the presence of numerous fatty emboli. When the injections were spread out over a period of time exceeding a week, the pathological changes were very characteristic of the condition as seen in man. While the lungs showed the greatest number of emboli, they were abundant everywhere. The capillary hemorrhages and areas of necrosis in the central nervous system and heart-wall were precisely like the small hemorrhagic areas of necrosis in the same organs of man. In the diaphragm and skeletal muscles the fatty degeneration of the muscle-fibres about groups of capillaries was very striking. Graham found this change only in the diaphragm, and says it does not occur in the skeletal muscles. In this he is mistaken; it may be found anywhere in the muscle-fibres bordering upon plugged capillaries.

In many of the animals receiving larger doses divided and given at intervals, the emboli in the systemic circulation appear to be more numerous than in the lung. It would seem that the lung takes up a certain amount of the oil and holds it back, but that some always gets through; and when the injections reach a certain degree there is an overflow into the systemic circulation. The proportions found in different organs vary with given animals, just as the symptoms produced by the injections vary widely. Local conditions of current, blood-pressure, and arterial resistance must have a great deal to do in determining the distribution.

As found by Graham and others, the fat is excreted in part by the kidneys, passing from the glomerular capillaries into the tubules. There is no evidence that the renal cells permit the fat to pass through. They never show the beautiful pictures of fatty degeneration seen in the muscles, liver-cells, and the cells of the adrenals and pancreas. A large amount of fat is also passed out through the lungs by way of the sputum. No one seems to have considered this avenue of escape, or to have used it as a means of diagnosis. As I shall show later, it is one of the earliest positive signs of fatty embolism.

It is apparent from animal experiments as well as from human pathology that the brain will stand a fairly large amount of capillary embolism before perivascular infiltration and necrosis occur. The gray matter may show great numbers of pure capillary emboli without any discoverable pathological changes; but as soon as these capillaries become more dilated, and a cord of fat extends farther back toward the longer branches and arterioles below, then other capillaries not containing fat show marked congestion, stasis, and thrombosis, with areas of degeneration and necrosis that quickly become filled with blood by diapedesis through the injured vessel wall. These small hemorrhages are nothing more than small hemorrhagic infarcts. The necrosis or degeneration occurs first; the hemorrhage is secondary.

A large part of the fat must be used up in the liver. Wherever there is a blocked-up capillary the neighboring liver-cells become filled with fat-granules and their nuclei stain less well, and finally the cell may become necrotic. The endothelium of the liver capillaries and the "Sternzellen" take up the fat first, and then pass it to the liver-cells. In an early stage the liver-cells may contain no fat, while the endothelium lining the intralobular capillaries appears as if set with minute beads. Sudan III and Scharlach R. sections of material from experimental animals present many beautiful examples of cell-activity.

Experiments 13 to 18.—These were carried out with injections of Sudan oil, given in the same way and in the same doses. The tissues are thus filled with an oil already dyed, and only the hæmatoxylin is needed to produce most beautiful pictures. In many ways the appearances thus secured are superior to those obtained by injecting the pure oil and staining the sections. We found, however, that the dye-oil causes a good deal of intravascular coagulation and thrombosis, particularly in the heart. A rapid injection of 2 to 3 Cc. of the dye-oil would often cause immediate death by the formation of a large, firm thrombus containing the greater part of the dye-oil. The pulmonary vessels were sometimes quickly obstructed. When used in divided doses, small ones of .2 to .5 Cc., there was often no apparent difference in action from that produced by the pure oil.

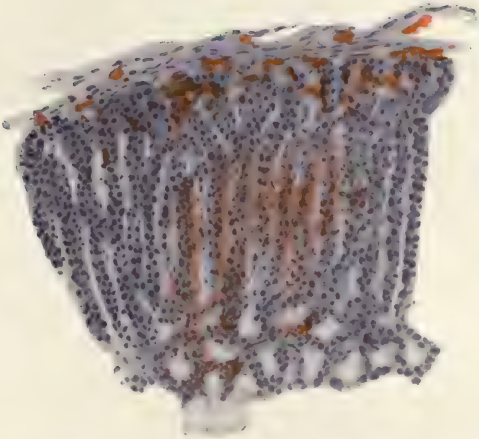
In using the dye-oil, the main object was to see if it would be taken up by the cells from the emboli in the capillaries; that is, an attempt was made to ascertain whether the fat in the cells giving the appearances of fatty degeneration derived these large fat-granules from its own invisible fat (true degeneration) or whether it was in reality an infiltration of fat into a dying cell. In the living tissues the dye-oil loses somewhat of its color, but never all in the time consumed by these experiments. The fat-droplets in the degenerating cells are, however, most of them paler than the emboli outside in the capillaries, and the cell-protoplasm tends to take on a diffuse red color. The majority of fat-droplets in the cells are perfectly colorless. This question has not been an easy one to decide; but my opinion is that the majority of the fat-granules in the degenerating cells are derived from the emboli in the capillaries, and that the process is essentially an infiltration into, or, in other words, a taking-up by, the damaged cells of great numbers of fat-droplets. There must exist then a peculiar attraction between the fat and the dying cells. A smaller portion of the finely-divided fat-granules in the cells comes from the cell itself.

Experiments 19 to 24.—Dogs were used to determine the effects upon the heart and circulation of injections of oil into the heart directly, into the jugular vein, and into a heart compensating for an artificially-produced valvular lesion. Tracings were made of the carotid, right auricle, and the jugular. The injection of 7 Cc. of oil directly into the heart causes a rapid fall of carotid pressure, and an increase in that of the auricle and jugular, as shown in the charts. Repeated injections cause large systolic pulsations in the right auricle, the arterial pressure steadily falls, and that of the auricle and jugular goes steadily up. Finally there is delirium cordis and death. The action of the fat-embolism is in all ways the same as that of air-embolism. The heart is unable to propel it onward, and there is finally delirium and cardiac paralysis.

In the case of fat-embolism of the heart in a case of compensated artificial lesion, as a tricuspid insufficiency, the injection of the oil causes a rapid break in the compensation, manifested by a great fall in the carotid pressure and a rise in auricular and jugular pressure. This is very well shown in the tracing made by Dr. Rous in the class of experimental pathology when he was teaching that course in my department some four years ago.

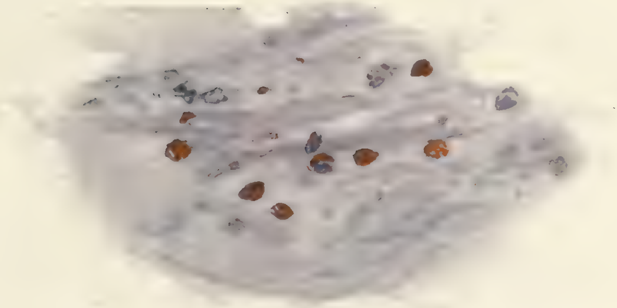
Experiments 25 and 26.—It was thought that a dye-oil made of the fat of the given animal might be more easily taken up by the cells of an animal of that species than a foreign oil. Scharlach R. chicken oil was accordingly used in experiments upon chickens. In these experiments it was found that minimum doses of the dye-fat caused almost immediate death. Smaller doses caused well-marked symptoms. Frozen sections showed pulmonary vessels injected with the red oil, marked pulmonary stasis, hemorrhage, and thrombosis. No appearances of fatty degeneration were found in the muscles, so that the point as to the taking up of the fat could not be definitely decided.

Fig. 12.



Section of adrenal showing multiple areas of hemorrhagic infarction and fatty degeneration due to fatty embolism. From case of fracture of both legs. Death ten hours after injury. Sudan III and hæmatoxylin stain of frozen section.

Fig. 13.



Alevolar cells loaded with fat-droplets. From sputum of case of fatty embolism showing marked pulmonary œdema. Fracture of femur. Death three days after injury. Sudan III.

ETIOLOGY OF FATTY EMBOLISM

From the literature we find that the entrance of fluid fat in large or small amounts into the blood stream and its lodgment in the capillaries of the lungs or systemic circulation are of frequent occurrence, and may be caused by the following:

1. All varieties of injuries to bones affecting the marrow, particularly fractures. The degree of injury may be marked or apparently slight. Comminuted fractures are the most dangerous. (See general bibliography.)

2. Surgical operations, such as amputations, brisement forcé, redressement, reduction of dislocations, resection, orthopædic manipulations, pressure upon atrophic spongiosa, use of chisel, concussion, etc. (See special bibliography.)

3. Concussion without fractures. (Ribbert, Flournoy, Gröndahl.)

4. Acute periostitis and osteomyelitis. (Flournoy, Jolly, Klebs, Wagner, Niederstadt, Gröndahl, Field.)

5. Hemorrhages into bone-marrow.

6. Presence of foreign body in marrow. (Riedel, Déjerine.)

7. Crushing, inflammation, or necrosis of adipose tissue in any part of the body (mastitis, removal of breast, ovariotomy). This leads to fatty embolism more rarely than does injury to the bone-marrow. (Ferguson, Riedel, Praeger, Pinner, Warnstedt, Fitz, Flournoy, Jolly, Bürger, Gröndahl.)

8. Rupture of fatty liver. (Hamilton, Zenker, Gröndahl, Engel.)

9. Childbirth. (Warthin.)

10. Lipæmia due to disease, as in diabetes, pancreatitis, gout, certain forms of anæmia, chronic nephritis, chronic alcoholism, acute fevers, chronic tuberculosis, splenitis, menstrual suppression, chronic diseases of liver, pancreas, and heart, general carcinomatosis or sarcomatosis, etc. In these forms of lipæmia the amount of fat in the blood is usually small, and the embolism is confined to the lungs and unimportant. (Sanders and Hamilton, Starr, Ebstein, Saundby and Barling, Fischer, Gröndahl, Degenhart, Rauch, Martens, Jürgens, Fraenkel, etc.)

11. Lipæmia due to intoxications, particularly with hæmolytic substances such as potassium chlorate, also with phosphorus, carbon monoxide, acute alcoholism, etc. Chloroform narcosis appears to

favor the development of fatty embolism. (Puppe, Romanow, Winogradow, Carrara, Bürger, Gröndahl.)

12. Fatty degeneration of thrombi, intima of blood-vessels (arteriosclerosis and atheroma) or heart, or of various cells gaining entrance to blood streams, etc. (Müller, Cohn, Lancereaux, Waldeyer, Egli.)

13. In cases of tetanus, eclampsia, delirium tremens, strychnine poisoning, and other convulsive affections. (Virchow, Gröndahl.)

14. In burns of the skin affecting the panniculus. (Carrara, Pacinotti, Gröndahl, Foa.)

15. Portogenous fatty embolism of liver. (Rössle, Gröndahl, Wiessel, Berner.)

Fatty embolism of clinical importance is in the great majority of cases due to injuries of the bones containing fatty marrow; less frequently it is caused by injuries to adipose tissue. Other forms of lipæmia and fatty embolism are of pathologic interest only, as the fat is of small amount, and the embolism usually limited to the pulmonary capillaries, causing no symptoms. Only in extremely rare cases does a fatty embolism of importance arise from any source other than the bones. It follows then that the greater the amount of fatty marrow in the bone the greater the chance for a serious lipæmia and resulting embolism; hence *osteoporotic* bones in old people or in younger individuals who possess *atrophic* bones from non-use (orthopædic conditions) are especially likely to yield on injury a sufficient amount of fat to cause trouble. Males are more frequently affected than females; adults than children. Repeated injury or concussion favors the entrance of fat into the blood stream. Fractures of the tibia and femur are the most frequent causes of fatty embolism. When many bones are broken, or there has been a severe concussion of the entire body, the fat may pass into the blood stream within a few seconds, and the symptoms develop almost immediately. In other cases the transportation of the fat may take place slowly and extend over a considerable period. In the case of osteoporotic bones direct pressure upon the ends may be sufficient to propel the fat into the blood stream. The amount of fat required to produce a fatal embolism is usually estimated at 1 Cc. per 1–2000 Gm. body weight. According to Scriba, 210 Gm. are necessary to cause fatal fatty embolism in man, but in a case reported by Fibiger 50 Cc. produced fatal cerebral embolism. Chloroform narcosis, tight bandages, massage, movements, jarring, etc., are regarded as favoring factors. Payr's theory that cases of lymphatic struma are especially liable to fatal fatty embolism has no foundation beyond that of coincidence in certain cases. As orthopædic manipulations are usually made upon children, and as lymphatic struma is frequently associated with orthopædic conditions (rhachitis), such coincidence might be expected to be frequent. The association of fatty embolism with death during chloroform narcosis may be explained in the same way as a result of the coincidence of the lymphatic constitution and orthopædic manipulation requiring chloroform, with death due to the lymphatism rather than to the fatty embolism. This would explain the very sudden deaths which occur during narcosis.

In general it may be said that our knowledge concerning the etiology of fatty embolism is more complete than that concerning its pathology, symptomatology, and treatment. The majority of the German writings upon the subject have been especially concerned with the etiology, and all of the earlier experimental work was carried out from this standpoint alone. Not until Scriba's paper appeared did the general pathology and symptomatology receive proportionate consideration; and in Gröndahl's recent monograph the other aspects of fatty embolism are for the first time adequately discussed.

PATHOLOGY OF FATTY EMBOLISM

From the study of the literature, the examination of my own cases, and experimental work with animals, the following statements concerning the pathology of fat-embolism can be made with some confidence that they express the true nature of the condition.

1. General Pathology.—*Entrance of the Fat into the Circulation.*—At the site of the bone injury there is often found a mixture of liquid fat and blood, or fat and pus. Fat-droplets may be detected in the discharges from the wound or from the incisions. In the case of osteoporotic bones cystoid cavities filled with liquid fat are found. From the broken fat-cells and fat-spaces the fat enters the open veins of the bone, the tension at the site of the injury usually being greater than that in the veins, so that the fat is readily forced into or taken up into the venous circulation. This may occur immediately

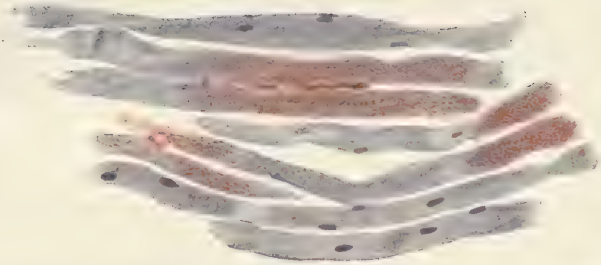
after the injury, or the taking up of fat may proceed for some time, so long as there is free fat at the seat of injury or until coagulation takes place. In addition to the fat taken up by the blood-vessels there is also an entrance of fat into the lymphatics, this occurring later than the direct entrance of fat into the circulation. The fat-droplets pass the regional lymph-nodes and enter the thoracic duct, thence pass through the venous circulation into the lungs. This passage of fat through the thoracic duct occurs usually some time after embolism of the pulmonary vessels from the fat gaining direct access to the veins. Hence an exacerbation of the symptoms is noted when this second supply of fat reaches the lungs, and, if the patient survives the first embolism, he may succumb to the second blocking up of the pulmonary and cerebral vessels. As the fat passes into the arterial system it may be forced through the systemic capillaries back into the veins and produce a definite cycle of symptoms.

2. The *tissue lesions* in fatty embolism and the consequent symptoms depend wholly upon the amount and distribution of the fat which has gained entrance to the circulation. It is evident that the latter factor is the more important. Three times as much fat might be poured into the blood stream of one individual with less effect than if one-third as much were injected into the circulation of another person. The result depends largely upon the destination of the emboli. It is, of course, evident that the larger the amount of fat in the blood the more likely are important regions to be overwhelmed by the fat. Evidently both individual and local factors serve to determine the course of the fat and its effects upon the organism.

Certainly the body, even the brain, can stand a relatively large amount of fat in its capillaries before the final limit of obstruction is reached and damage to the tissues ensues. In all cases of fatty embolism of the lungs some fat reaches the kidneys and is excreted. It must also reach the brain and, temporarily at least, lodge in some of its capillaries. But miliary hemorrhagic infarctions of the brain occur only when there is a marked degree of obstruction, stasis, and secondary thrombosis. The same thing is true of all the other organs of the body.

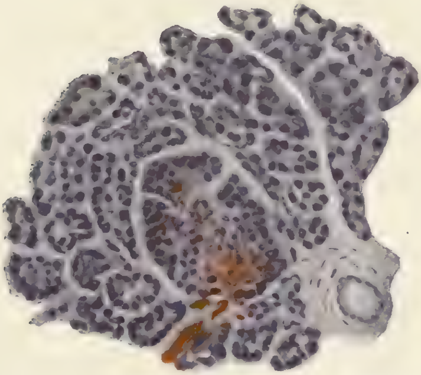
There is not a single organ or tissue in the body—be it thyroid, pancreas, adrenal, testis or skeletal muscle—that does not get some fat in its capillaries during a fatty embolism. (Figs. 1–15.) Ana-

Fig. 14.



Portion of muscle of leg showing fatty emboli and fatty degeneration of the muscle-fibres about the emboli. Sudan III and hæmatoxylin.

Fig. 15.



Portion of pancreas with area of Langerhans showing fatty emboli and fatty degeneration of cells of the island lying near the emboli. Sudan III and hæmatoxylin.

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tomical considerations and the peculiar organization of tissues will determine the result. As the fat enters the venous circulation first, the heart and the lungs first bear the brunt of it. When the fat suddenly enters the blood stream in large amounts, the effect upon the heart may be the same as in air-embolism. The cardiac contractions are insufficient to drive the fat on into the lungs, and it remains in the right ventricle, increasing perhaps in amount, and exciting the formation of fibrin. The heart may gradually be exhausted, delirium may ensue, and sudden death. It is extremely likely that many of the cases of death within twenty-four hours after an injury are the result of cardiac paralysis.

The heart is further impeded in its action by emboli within its own vessels. A vicious circle may thus be set up, and the organ become more and more embarrassed. With the formation of fat-emboli in the coronaries local infarctions of the heart muscle are likely to occur, and these serve to bring about the final break in cardiac efficiency. In such cases there is a great fall in arterial pressure, and a corresponding rise in the venous; the heart-rate is very rapid and irregular. It is, therefore, proper to speak of a *cardiac symptom-complex* in fatty embolism. The importance of this has been strangely overlooked before. The autopsy findings of cardiac conditions support the belief that it is not rare. Colley and a few other observers are the only ones who have regarded the part played by the heart as of any consequence.

In all cases the pulmonary capillaries get the greater share of the fat-emboli, but the lung is better able than any other organ to withstand this condition. Nevertheless, as not infrequently happens, the lung is overflooded, and so many of its passageways are blocked that a *respiratory symptom- and pathologic-complex arises,* as shown by cyanosis, dyspnœa, pulmonary œdema, hemorrhage, and hemorrhagic infarction. Beyond the lung, in the systemic circulation, any one organ may receive the greatest damage from the emboli. If it is the brain, then there occurs a *cerebral symptom- and pathologic-complex,* easily recognized clinically and at autopsy. Congestion, stasis, thrombosis, hemorrhage, hemorrhagic infarction, and areas of degeneration characterize the cerebral lesions. Headache, vomiting, restlessness, apathy, clouded sensorium, diminished reflexes, low or high temperature, delirium, paralysis, coma, convulsions, and death result from these lesions. Yet, if not too severe, recovery may take place.

The blocking of the glomerular capillaries of the *kidney* does not produce any appreciable lesion in this organ. Slight hemorrhages, congestion, stasis, etc., are occasionally seen, but no marked degenerative lesion.

In the *adrenals* there may be extensive blocking, hemorrhagic infarction, and fatty degeneration. We cannot yet recognize clinically such an *adrenal symptom-complex,* and we do not know what part these lesions may play in the cardiac disturbance. The extreme fatty change in the *liver* may be in part a protective function.

Likewise in the *pancreas* the island of Langerhans may be blocked with fat-emboli, and the cells of the island be markedly infiltrated with fatty granules. What disturbances may be caused by this we do not yet know. The same thing is true of the *thyroid.* There is extensive blocking of the capillaries of this organ in fatty embolism, but we cannot recognize any effects, although some functional disturbance must occur.

Fatty change in the *diaphragm* may be associated with disturbances of circulation and respiration. In the *skeletal muscles* numerous areas of fatty degeneration and embolism may account for some of the general malaise and fever. In all of these minute damaged areas protein change must be going on, and various intoxications may be secondary to the embolism. Emboli occur also in the capillaries of the *stomach, intestine, bladder, lymph-nodes, thymus,* blood-spaces of the *spleen,* etc., without causing recognizable tissue-changes.

We recognize, therefore, at the present time only three chief *lesion-* and *symptom*-complexes in fatty embolism: *cardiac, pulmonary,* and *cerebral.*

The action upon the blood must always be borne in mind. In some cases an active hæmolysis takes place, and a large amount of blood may be lost. Blood-pigment casts may be present in the urine.

3. The minute areas of tissue infarcted by the fatty emboli show in certain organs, such as the heart, skeletal muscles and diaphragm, liver, adrenals, pancreas, and spleen, an especial tendency on the part of the injured parenchymatous cells to take up fat-droplets. This tendency is not similarly shown by the thyroid, kidneys, brain, salivary glands, testis, etc. There must exist some especial attraction

between the fat of the emboli and the injured protoplasm of these cells. In the case of the liver it is worth noting that this "fatty degeneration" or agonal fatty infiltration occurs chiefly about the emboli in the capillaries which flow into the central veins, but may also be found anywhere in the lobule and at the periphery.

4. The *excretion* of the fat is chiefly through the kidneys, in periodical cycles, in accordance with the movement of the fat from the arterial to the venous side and back again. The passage into the tubules is accomplished in the glomeruli, and not in the epithelial cells of the tubules. Phagocytes also convey the fat-droplets out of the body in great numbers, especially in the sputum, fæces, and bile. No doubt much of the fat is utilized by such organs as the liver.

5. SPECIAL PATHOLOGY.—*Lungs.*—The *macroscopic* changes characteristic of fatty embolism are: Œdema, congestion, hemorrhage, hemorrhagic infarctions, acute emphysema, and the presence of oil-droplets in the larger vessels. The *microscopic* changes are: Fatty emboli in larger and smaller vessels, as a rule evenly distributed throughout the lungs, the capillaries being dilated to two to six times their normal diameter, and the fat confluent in branching cylinders corresponding to the course of the capillaries. In the larger arterioles the fat-droplets often form spherical masses that are not confluent. Œdema, hemorrhage, congestion, hemorrhagic infarction, blood-plate and fibrin thrombi, bronchopneumonia, and emphysema are the chief secondary changes seen microscopically. Emboli of bone-marrow cells are also numerous. (Figs. 1 and 2.)

Heart.—Macroscopically the presence of fat in the subepicardial vessels may be recognized. Both ventricles, usually the right more markedly, are dilated, and miliary hemorrhages and patches of fatty degeneration are seen in the heart muscle. *Microscopic* examination shows the presence of fat-emboli in great numbers in the blood-vessels, and in the immediate neighborhood of these the heart muscle may reveal localized fatty degeneration of a peculiar kind (numerous large droplets), congestion, hemorrhage, thrombosis, and small anæmic infarcts. It would seem that some of the fat in the muscles is not the intrinsic fat of the cell thrown into view as a "fatty degeneration," but is taken up by the injured muscle-cell from the neighboring fat-emboli. (Figs. 6, 7, and 8.)

Brain.—Macroscopically the brain shows scattered miliary hemorrhages ("cerebral purpura" of Schmidt), most abundant in the white matter and near the ventricles, and often found in groups. *Microscopically* the small hemorrhages are found arranged around vessels filled with fat; these are surrounded by a small area of necrotic or degenerating brain tissue, outside of which is an encircling zone of red cells, giving the hemorrhage a wreath shape. The majority of these hemorrhages are the size of a pin-head, although some are larger. They are minute anæmic infarcts within a hemorrhagic zone. Fibrin thrombi are also found in some of the vessels, usually in association with the fat-emboli. According to the literature (Gröndahl, Ribbert, etc.), these hemorrhages do not appear until two or three days after the injury. I have found them abundantly in a patient dying twelve hours after fracture of the bones of the leg. (Figs. 3, 4, and 5.)

Cord.—The *macroscopic* and *microscopic* appearances of the cord are similar to those of the brain, but the lesions are fewer and less marked.

Kidneys.—Macroscopically the kidney usually shows only congestion. *Microscopically* the fat-emboli are found particularly in the capillaries of the glomeruli; a much smaller amount of fat being present in the intertubular vessels. Congestion and small hemorrhages are usually present, but degenerative changes are not the rule. Very rarely are fat-droplets found in the tubules. (Fig. 10.)

Skin.—Miliary hemorrhages in the skin sometimes occur in severe fatty embolism. These hemorrhages take place about vessels filled with fat, and the obstructed blood-vessel shows fatty degeneration of its wall.

Striated Muscles.—These show changes similar to those in the heart muscle: Fat-emboli, miliary hemorrhages, and localized marked fatty degeneration about the vessels containing emboli. In the case of the voluntary muscles, the taking up of fat from the emboli is even more decided than in the case of the heart muscle. (Fig. 14.)

Liver.—Macroscopic appearances are those of passive congestion. *Microscopically:* Fat-emboli in the capillaries, and localized fatty degeneration or infiltration. (Fig. 9.)

Spleen.—Macroscopically: Congestion. *Microscopically:* Congestion and numerous fatty emboli without other recognizable changes.

Pancreas.—Numerous emboli in capillaries of the island of Langerhans, without other recognizable charge. (Fig. 15.)

Adrenals.—No *macroscopic* changes. *Microscopically:* Numerous fat-emboli in capillaries of cortex, with localized fatty change in parenchymatous cells. (Fig. 12.)

Thyroid.—Numerous fatty emboli. Deficiency of colloid. No other recognizable change. (Fig. 11.)

In all other organs and tissues more or less numerous fatty emboli without recognizable change.

PATHOLOGIC TECHNIC

For the recognition of fatty embolism the fresh material should be cut on the freezing microtome, stained with Sudan III, Scharlach R., or osmic acid, and mounted in glycerine-gelatin; or formol may be used as a fixing agent. After formol fixation the material may be cut on a freezing microtome and then stained with the various fat-dyes mentioned. Flemming's solution or one per cent. osmic acid may be used to fix tissue containing fat-emboli; the osmic acid acts only upon the oleates. When fat-containing tissues are imbedded in celloidin or paraffin, the process of imbedding should be carried out as quickly as possible; chloroform or benzene should be used in place of xylol.

1. STAINING OF FAT WITH OSMIC ACID

1. Fix in formol twenty-four hours.
2. Wash; freeze; cut.
3. Place sections in one per cent. osmic or Flemming's solution one to twenty-four hours.
4. Wash in water, changing frequently.
5. Eighty per cent. alcohol one-half to two hours.
6. Wash in water.
7. Place section flat on slide; blot; add a drop of warmed glycerine-gelatin; cover quickly.

To mount in balsam: After 6, counterstain with hæmatoxylin or safranin; wash again; dehydrate quickly with absolute alcohol; clear in pure benzene; mount in pure melted Canada balsam (containing no xylol).

2. STAINING WITH SUDAN III OR SCHARLACH R.

1. Formol fixation twenty-four hours; cut on freezing microtome.
2. Sections in seventy per cent. alcohol.
3. Stain in acetone or alkaline alcoholic solution of Sudan III or Scharlach R. for two or three minutes; in the simple solution twenty to thirty minutes.
4. Wash in fifty to seventy per cent. alcohol, differentiating as needed.
5. Transfer to water; thence to slide; blot; and mount in glycerine-gelatin.

For a nuclear counterstain put the sections in water after 4; then stain in hæmatoxylin; differentiate quickly in acid alcohol; wash in water; place in weak ammonia or lithium-carbonate solution; wash in water; transfer to slide; blot; mount in glycerine-gelatin.

Staining solutions of Sudan III or Scharlach R. are made as follows:

1. Dissolve stain in seventy to eighty per cent. boiling alcohol; keep in the incubator over night; use warm.
2. Make a solution of absolute alcohol 70 Cc., ten per cent. caustic soda solution 20 Cc., water 100 Cc. Saturate with stain, warming gently.
3. Make a solution of seventy per cent. alcohol 50 Cc., pure acetone 50 Cc.; saturate with stain.

Sudan III and Scharlach R. stain the smallest particles of fat yellowish-red to deep scarlet. Scharlach R. on the whole gives the best results, and especially good pictures are obtained when contrasted with hæmatoxylin.

SYMPTOMATOLOGY

The symptoms of fatty embolism vary greatly, accordingly as the brain, lungs, or heart receives the greatest number of emboli, and shows a corresponding disturbance of circulation. The earlier observers concerned themselves with fatty embolism of the lungs alone, and failed to examine the brain, or to consider the possibility of a fatal cerebral fatty embolism. Not until Scriba's paper appeared was the importance of fatty embolism of the brain recognized. His dictum that the fatal outcome of any case of fatty embolism is always due to a plugging of the cerebral vessels was generally accepted for a time, and led to more careful examination of all the organs and tissues after death from fatty embolism. As a result of the more recent studies Scriba's view has been proven to be incorrect; and, while the great importance of cerebral fatty embolism is recognized, two clinical types of fatty embolism are distinguished: A *pulmonary* and a *cerebral*. It is also possible that in some cases a *cardiac* type may be differentiated.

Pulmonary Fatty Embolism.—In its symptoms and course this is clinically less characteristic than the cerebral, and its diagnosis correspondingly more difficult. The chief symptoms are respiratory: Dyspnœa, cough, cyanosis, pulmonary œdema, and hemorrhage. These symptoms may develop immediately after the bone injury (apoplectiform cases), or their development may be slow. The respiratory symptoms may or may not predominate. In many cases it is impossible to make a diagnosis until an autopsy is performed. Death may taken place almost immediately, or the patient may live for several weeks. There may be an initial free interval before the respiratory symptoms appear. Restlessness, headache, and stupor may be the first symptoms; or a respiratory difficulty may suddenly develop, and the patient suffer from most severe air-hunger. The heart-rate is increased, the rhythm irregular, and the tension low. Precordial or epigastric pain may be felt. The right heart, especially, is dilated. The temperature may be low or high; more frequently it is low at first and rises gradually after a few hours. The respiratory rhythm may be irregular; the resonance is slightly diminished, and becomes somewhat tympanitic in character. Moist râles are heard over the base, and there is marked pulmonary œdema, the sputum often running from the mouth in a foamy mass. Often it is blood-stained, and free fat can be demonstrated in it by staining with Scharlach R. Fat appears also in the urine.

In fatal cases asphyxia may rapidly develop, following closely upon the trauma, and the patient dies in apparent collapse. Between the fatal and the non-fatal cases there is no sharp line; nor is there such between the respiratory and cerebral forms. The first form usually comes on soon after the trauma, but may be delayed, while the cerebral variety develops later, although it also may appear within a few hours. In the respiratory form cerebral symptoms may develop as the result of anæmia of the brain and carbonic acid increase in the blood.

The *cerebral* form usually manifests itself after an intervening period, often three to eight days, but may come on within a few hours. In these cases the pulmonary lesion is less prominent than the blocking of the cerebral vessels. The patient's first symptoms are uneasiness or headache, drowsiness, mental cloudiness, stupor; sometimes there is vomiting, often hallucinations or delirium passing into a somnolent or comatose state. The skin is pale and may show petechiæ, and the lips are bluish. Reflex excitability is gradually lost, and there may be definite spasms, tremors, convulsions, or paralysis (even hemiplegia). While signs of cortical irritation are usually present, those of increased intracerebral pressure, such as choked disk, slow pulse, and rigidity of neck, are invariably absent. The respirations are greatly increased, and cyanosis and dyspnœa may be marked. Symptoms of the respiratory form are usually added to those of the cerebral. The Cheyne-Stokes phenomenon is often present. The pulse becomes very rapid, weak, and irregular. At the beginning the temperature may fall, and may remain subnormal to the end; more frequently there is a rising temperature curve reaching to 104° to 105° before death, and sometimes persisting at this height for several hours postmortem. In many cases the symptoms show three distinct stages: A free interval, a soporific stage, and a comatose. In the cases that recover there may be only the first two stages.

In both forms free fat may appear in the urine, but is most abundant in the cerebral form, giving evidence of the flooding of the arterial system with fat. It appears periodically, as described above. It may form an actual layer on the surface of the urine, or a small number of fat-droplets alone may be seen floating on the surface. Associated with the fat there may be red blood-cells, casts of different types, particularly blood-casts containing fat-droplets. Albumin may or may not be present. If there is pulmonary œdema, fat-droplets will be found in the sputum. The blood also should be examined for fat-droplets.

It is evident that in all cases in which there is fat in the urine some fat must also reach the brain, and the occurrence of cerebral symptoms depends upon the amount of fat reaching that organ. It is highly probable that in all cases of fatty embolism some fat must get into the cerebral circulation. If the amount is small, and if the capillaries are blocked for so short a distance that no serious disturbance of the nutrition of that part is produced, it is unlikely that there will be any serious cerebral symptoms, or at most only transitory ones. The normal lung can bear a great deal of fatty embolism without damage; and the same is true in a lesser degree of the brain.

DIAGNOSIS

Fatty embolism may be mistaken for shock, collapse, *commotio cerebri, contusio cerebri, compressio cerebri,* hysteria, intracranial hemorrhage or inflammation, acute or chronic alcoholism, delirium tremens, sunstroke or heat-exhaustion, diabetic or uræmic coma, septicopyæmia, etc. At times the diagnosis may be easy; at other times it is extremely difficult to differentiate between fatty embolism and some of these conditions, notably intracranial hemorrhages. When the patient has received injuries about the head the difficulty of differentiation becomes greater. Consideration of the temperature, heart's action, pulse, respiratory, and cerebral symptoms is of little avail, as practically all the clinical phenomena characterize these various conditions in common, and it becomes impossible to separate them. The occurrence of a free interval in many of the cases of fatty embolism will distinguish them from shock, *commotio cerebri* and *contusio cerebri.* In the case of meningeal hemorrhages and *compressio cerebri* the differential diagnosis is at times very difficult. In fatty embolism the cerebral symptoms are more diffuse, the centres are not affected regularly, or as a part of a definite system. Choked disk and the other signs of increased intracranial pressure are not seen.

In general the diagnosis of fatty embolism should rest upon those considerations that are peculiar to it alone. In the first place, it should always be looked for after any damage to bones containing fatty marrow, no matter how mild this injury or concussion may appear to be, also after orthopædic manipulations of atrophic bones. If after such operations or injuries symptoms of restlessness, sleepiness, and coma develop, with dyspnœa, cough, and signs of pulmonary œdema, then the diagnosis of fatty embolism is very probable and the objective signs of this condition—*fat in the urine* and *fat in the sputum*—should be positively determined. The presence of fat in the blood may also be ascertained by examination of the retinal vessels, or by removal of a large amount of venous blood.

Fat in Urine.—Riedel and Scriba were the first to show that fat-droplets appear in the urine after the majority of bone injuries. Other writers have reported negative findings. It must be borne in mind that lipuria is often delayed for several hours or days, and that the patient may die before it occurs; also that lipuria is usually intermittent. There may be a layer of fat on the surface of the urine, or only large fat-drops.

New Diagnostic Sign.—The presence in the sputum of free fat-droplets and of numerous phagocytes containing an abundance of fat-granules is here put forth as a new and extremely valuable diagnostic aid. In 1906 I began to teach my classes that fat in the sputum is an important and early sign of fatty embolism of the lungs, basing my belief upon a case I had seen in which an old man, after a fracture of the femur, showed sputum containing blood and large numbers of fat-droplets. Carrington (1908), quoted by Le Conte and Stewart, is the only other writer who, so far as I have been able to discover, mentions this sign. He is quoted as having found it in six cases. Gröndahl does not mention it. I have confirmed this finding in all cases of fatty embolism which I have recently seen, hence regard it as a most valuable sign. Fat escapes by rupture from the dilated capillaries of the lungs before it passes from the kidneys. If the pulmonary obstruction is at all marked the amount of sputum will be increased, and in this sputum will be free fat-droplets and alveolar cells containing large fat-droplets. Stain the fresh unfixed sputum under a cover-glass with Sudan III. Occasionally cells containing fine fat-granules are found in ordinary sputum; after pneumonia they are more numerous, and small fat-droplets may then be found free. They are never as large or numerous as in fatty embolism.

The differential diagnosis of fatty embolism chiefly depends, therefore, upon the following factors:

1. Injury to bone-marrow or adipose tissue.
2. A cardiac, pulmonary, or cerebral complex of these combined (restlessness, stupor, coma, dyspnœa, cough).

3. Free fat-droplets in sputum: Fat-containing alveolar cells in sputum.

4. Free fat-droplets in urine.

5. Examination of eye-grounds for evidences of fat in circulating blood.

6. Examination of venous blood for fat-droplets.

7. Increase of temperature, rather than a lowered temperature as reported by Scriba, and as quoted in the text-books.

8. Examination of skin for petechial hemorrhages.

COURSE

The course of fatty embolism may be rapid or slow. The cases are described as *apoplectiform,* with fatal result at once or within a few hours; or the symptoms and signs may persist for several days or weeks, then to terminate fatally or in recovery. In apoplectiform cases the diagnosis may be possible only through the autopsy, as there may be no time for the development of a clinical picture presenting characteristic symptoms.

PROGNOSIS

The prognosis in well-developed cases of fatty embolism with recognizable signs and symptoms is grave. The majority die; the number of reported recoveries is small. It is probable, however, that the literature concerning this condition cannot be taken as a criterion of its prognosis. The cases that recover are probably not recognized as fatty embolism, but pass under the diagnoses of shock, collapse, concussion, etc. It is my own belief that a larger proportion of cases of fatty embolism do recover. A more careful observation of patients suffering from fractured bones will, I am sure, support this view.

TREATMENT

The treatment of fatty embolism is both *prophylactic* and *therapeutic.* The *preventive* treatment in the case of fractured bones is absolute rest and the avoidance of all unnecessary moving of the patient. Particularly is transportation over rough roads, or in a jolting vehicle, or even transportation for a long distance under any conditions, contra-indicated, because of the fatal outcome apparently induced by such motion, as reported in the literature. Massage and tight bandages are also dangerous, as they increase the tension at the site of the injury and promote the propulsion of fat into the veins and lymphatics. In the case of orthopædic operations, particularly when there is disuse atrophy and osteoporosis of the bones, direct force upon the atrophic spongiosa, either by the use of the chisel to the bones or by direct pressure upon them, should be avoided. In all operations upon osteoporotic bones the saw should be used rather than the chisel, and concussion should be guarded against. The slow removal of the Esmarch bandage is also recommended by von Aberle, Gröndahl, and others. Especial care should be taken in orthopædic manipulations upon children of lymphatic constitution.

Reiner advises the puncture of the femoral vein, or the insertion of a cannula through the saphenous into the femoral, after bloodless orthopædic operations, so that when the Esmarch bandage is slowly removed the wave of blood flowing into the veins will wash out any fat that may be in the vessels. Lexer was unable to demonstrate the presence of fat in blood obtained in this way from the saphenous vein. Other writers are not enthusiastic over the method.

Lexer states that the most effective prophylactic against the occurrence of fatty embolism in orthopædic operations is to avoid the use of the chisel upon the spongiosa, and that a saw should always be employed in such operations as the bone may be sawn through without crushing or concussion. Further, he issues a warning concerning the employment of pressure upon the articular ends of bones in operations upon crooked limbs, particularly when the ends are atrophic and softened.

Ligation of the veins above the injury or seat of operation in such conditions as thrombophlebitis is also recommended for the prevention of infected emboli. By some surgical writers this is not considered a practical measure. In comminuted fractures free incision and drainage of the fat at the seat of injury, also incision and removal of stitches to relieve the tension, are recommended as preventive measures.

Therapeutic Measures.—After fatty embolism has occurred the treatment consists of measures to get rid of the fat in the blood stream by proper stimulants. Among the methods advised for the removal or neutralization of the fat in the blood stream are the following:

1. Injections of two per cent. sodium carbonate solution. Czerny's experiments with this method were fruitless in so far as saving the life of the animal was concerned, although the dyspnœa seemed temporarily lessened. In one human case in which I saw this treatment given there was great lessening of the air-hunger, but the patient died. Minnich regards it as useless. It needs, however, a more thorough trial than has yet been given it.

2. Czerny recommended venesection to lessen the venous congestion, and also advised the injection of sodium carbonate solution after the bleeding. Temporary benefit at least may be obtained in this way.

3. Injections of physiologic salt solution into the veins are recommended by Schanz (1910). Eight out of ten cases of fatty embolism following orthopædic manipulation were treated by Schanz with saline infusions, the solution being injected at several points in order to accomplish most effectually the desired dilatation and flushing of the veins. If the symptoms are severe the saline solution should be injected directly into the large veins. The earlier the infusion and the larger the amount of salt solution injected the better the result. Schanz's success with this method is very promising, and it should be given a thorough trial. At least, it is easily carried out and can do no great harm. Gröndahl doubts that Schanz's cases were really fat-embolism, but this doubt does not seem well grounded. Lesser made an experimental therapeutic study of the effects of the injections of salt solution directly into the right ventricle in air- and fat-embolism, and recommends saline injections as a therapeutic measure in man.

4. *Drainage of Thoracic Duct.*—In 1910 Wilms recommended the establishment of a thoracic duct fistula in the treatment of fatty embolism, on the ground that more fat is added to that in the blood by absorption through the lymphatics, the fat passing the lymph-nodes and reaching the thoracic duct, whence it passes into the venous circulation some time after the fat that gained immediate entrance into the veins. This accession of fat may be the final straw in bringing about the fatal termination, and if this increase of fat in the blood stream can be prevented the patient may survive.

Wilms performed this operation in one case of fatty embolism in a patient who fell from a window. Sixteen to twenty hours after the operation the patient became soporific, temperature rose to 39° C., respirations 40. Believing the entrance of the fat to be chiefly through the lymphatics, Wilms opened and drained the thoracic duct, large fat-droplets appearing in the lymph. The fistula closed on the ninth day, and the patient gradually recovered. Wilms's method was used experimentally by Fritzsche (1910), who found that drainage of the thoracic duct warded off danger if performed at the first sign of trouble. Gröndahl, however, found experimentally that ligation of the femoral vein and removal of the inguinal lymphatic tissues did not prevent the occurrence of fatty embolism. Nevertheless, he thinks the method advocated by Wilms and Fritzsche is theoretically the best one in all cases in which there is a free interval with symptoms of cerebral embolism developing. He would consider the symptoms of a beginning cerebral embolism as indications for the establishment of a thoracic duct fistula, and that the operation should be performed as quickly as possible. The risk of the operation itself is slight, and the consequences negligible. On the other hand, as so few cases of fatty embolism diagnosed *intra vitam* live, the risk of the operation is nothing compared to that of the fatty embolism itself. As Gröndahl says, this method of treatment is certainly theoretically a good one, and surgeons should be urged to carry it out whenever there are indications of cerebral fatty embolism.

The combination of venesection, saline injection, and thoracic duct fistula may then be advised as offering at the present time some hope in the treatment of fatty embolism. All other treatment must be directed toward the prevention of further entrance of fat into the blood stream, and the relief of the dyspnœa by lessening the work thrown upon the lungs and heart. Cardiac stimulants, the administration of oxygen, artificial respiration, etc., are chief among other measures to be tried.

MEDICOLEGAL SIGNIFICANCE

The medicolegal significance of fatty embolism has been discussed by Wintritz, Puppe, Westenhoeffer, Bürger, Gröndahl, and others. Many questions of great interest are involved. From the literature the following points may be accepted as authoritative:

1. Fatty embolism of lungs, brain, and kidneys is always an *intravital phenomenon.* It does not occur in the capillaries of these organs after death; although putrefactive gas-emphysema may cause the entrance of fat into the large vessels, it cannot propel it into the small vessels of these organs, nor can burning after death cause this.

2. Fatty embolism in the lungs, brain, or kidneys of a person whose body has been burned must be taken as evidence that there was previous to death some injury to fat-tissues or bone-marrow, or severe concussion of the bones.

3. Fatty embolism as a cause of death after trauma must be excluded by autopsy examination before a diagnosis of death from acute alcoholism, intracranial hemorrhage, meningitis, insanity, hysteria, shock, etc., can be given. Particularly when there is any suspicion of foul play should this condition be looked for and considered as a cause of death. In my Case XI above cited, a fatal case of fatty embolism in a man who was thought to have been pushed down stairs was diagnosed as "acute alcoholism" by the coroner, and no investigation was ever made.

4. Fatty embolism is of medicolegal importance, therefore, as a cause of death, also as an indication whether a burned body had been injured in any other way before the burning. The criminal and insurance aspects of the question are obvious.

CONCLUSION

Fatty embolism should be looked for after all bone injuries and after orthopædic manipulations. Mild cases are probably very common, and fatal cases are certainly much more numerous than is suspected. The general failure of text-books and practitioners to recognize the importance of this condition is sufficient reason for a complete presentation of its etiology, pathology, symptomatology, and treatment.

NOTE.—This monograph was prepared in book form in 1907. Having deferred its publication, it has now been condensed and brought up to date.

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Miliary Tuberculosis of the Placenta

With Incipient Pulmonary Tuberculosis of the Mother Becoming Latent after Birth of Child

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MILIARY TUBERCULOSIS OF THE PLACENTA

WITH INCIPIENT PULMONARY TUBERCULOSIS OF THE MOTHER BECOMING LATENT AFTER BIRTH OF CHILD

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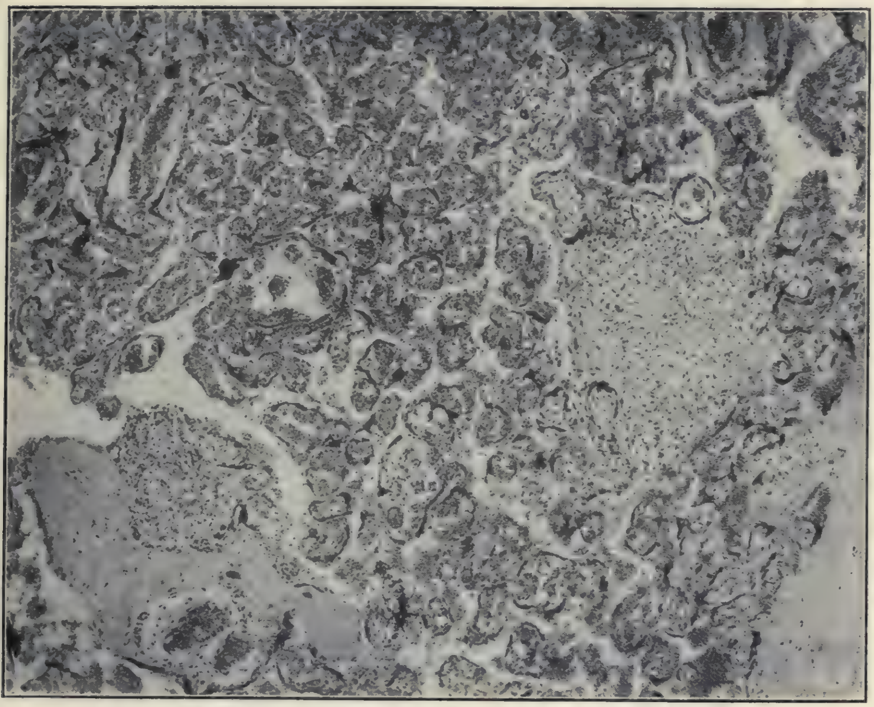
The case recorded here is of great importance in that it demonstrates the possibility of the transmission of tubercle bacilli to the fetus from a mother having an unrecognized latent tuberculosis of one apex. In the cases of placental tuberculosis recorded in the literature up to the present time there is no reported instance of such an occurrence; all of the cases of placental tuberculosis are given as occurring in association with advanced pulmonary or acute miliary tuberculosis of the mother. Tubercle bacilli, however, have been demonstrated by the antiformin method in placentas coming from mothers with incipient tuberculosis of the lungs, but no histologic evidences of tuberculosis were found in such placentas, and no congenital transmission of the disease to the offspring has been shown beyond doubt to occur in such cases.

It has been generally assumed that the entrance of tubercle bacilli into the blood-stream and their lodgment in the placental sinuses is a rare event, likely to occur only in pregnant women showing a late stage of pulmonary tuberculosis. If it can be shown that in pregnant women who have incipient pulmonary tuberculosis lesions the bacilli may enter the circulation under the influence of pregnancy and cause a miliary tuberculosis of the placenta or congenital infection of the fetus, the sociologic and eugenic aspects of the transmission of tuberculosis from parent to child become greatly increased in importance. It is generally recognized that the influence of pregnancy on maternal tuberculosis is bad; and observations are only too frequent of the kindling of incipient and latent pulmonary lesions and the exacerbation of more severe processes through this factor. While the majority of writers on tuberculosis concede that pregnancy acts unfavorably on the disease so far as the mother is concerned, practically all unite in minimizing the dangers of congenital transmission to the progeny of such tuberculous mothers, and this in spite of the not slowly accumulating cases of placental tuberculosis. For that reason especially I regard this additional case of placental tuberculosis discovered in my laboratory as of very great importance in throwing more light on the possibility of such a transmission.

All placentas obtained in Dr. Peterson's obstetric clinic in the university hospital are subjected to a routine gross and microscopic study in the pathologic laboratory. During the course of such routine examination, a placenta sent to the laboratory on Oct. 28, 1912, was found by me, on microscopic examination, to contain miliary tubercles in practically every section. Inasmuch as the history of the mother sent with the placenta made no mention of the existence of tuberculosis or the possibility of such disease in her, my interest was at once excited in the case, and it was studied from all possible angles. The history of the mother as given was entirely negative as to tuberculosis, as follows:

Miss A. B., a domestic, aged 20, was admitted to the University Psychopathic Hospital in February, 1912, with "hysteric insanity." At the age of 18 she had measles and scarlet fever and since has been very "nervous." There is no family history of tuberculosis and the patient, so far as she knows, has never been exposed to the disease. When she entered the hospital she gave a rather definite history of gonorrhea. Physical examination in other respects was negative except that she was found to be pregnant and was referred to the maternity ward, where after an apparently normal pregnancy she gave birth to a viable child on October 28. The placenta was tagged with the mother's name as soon as delivered and the course of the specimen is known without chance for error. When the diagnosis of miliary tuberculosis of the placenta was returned the mother was referred to the medical clinic for a thorough examination. The findings again were negative except that at times the pulse-rate was rather rapid (108) and on exertion she had a slight dyspnea.

Examination (by Dr. Hewlett Nov. 13, 1912).—Patient was referred for chest examination on account of miliary tubercles having been found in the placenta. Examination of chest shows that the right apex behind shows slight increase in fremitus, beyond the normal difference, slight impairment on percussion and somewhat harsh expiration. There are no râles. No active tuberculosis is found in the lungs, but there is some suspicion of a healed process at the right apex.



Two miliary tubercles from placenta ; one, at the right, is healing : at the left is one more recent, epithelioid and situated on the chorionic stem ; a latent lesion was in right apex of mother.

Examination (by Dr. Schmidt).—Eyelids are slightly puffy; hands are cold and clammy, with slight cyanosis of the finger tips. No enlarged lymph-nodes are found in the neck. The right upper chest expands less than the left. Litten's sign is not seen on either side. The right upper is not so full below the clavicle as is the left upper. Expiration is rather harsh over the right upper in front. The back shows slight impairment over the right upper with slight increase in tactile fremitus, as well as of whispered and spoken voice. Expiration is somewhat increased over the right upper behind. No râles are heard.

Tuberculin Tests.—There is a slight reaction to 25 per cent. in ninety-six hours (von Pirquet).

Subcutaneous Test.—Two mg. of tuberculin were injected at 10 a. m., November 5; at 2 p. m., November 6, there was slight redness around area of injection, and area was very tender. Highest temperature was 99.2 F. Dec. 7, 1912, patient was given 5 mg. of tuberculin, subcutaneously. On noon of the following day, temperature reached 99.7 F., falling to normal toward evening. The area of injection was red, indurated and tender. No râles were heard.

Roentgenoscopy reveals slight increase of root shadows but no definite sign of tuberculosis.

Medical examination shows a positive tuberculin test, a suspicious right apex, but no evidence of active disease.

From these examinations it is evident that the patient has had an incipient tuberculosis of the right apex, now no longer active. It can be inferred that earlier in pregnancy this apical lesion was active for a time, and that bacilli then escaped into the blood-stream and into the interchorionic spaces. This assumption is supported by the character of the placental lesions. In practically every section made of this placenta there were miliary tubercles, in all respects characteristic histologically. The average section contained from four to six tubercles. Very few of these tubercles were recent ones. No absolutely fresh miliary thrombi, such as characterize the early miliary tuberculosis of the placenta, were found. The majority of the tubercles were epithelioid in type with a tendency to healing, as shown by the development of a more mature connective tissue in and about the tubercle, some of the tubercles appearing more fibroid than the connective tissue of the villi. Giant-cells were not frequent. Many of the tubercles showed no caseation or only a slight central caseous change; only a few showed a marked central caseation. Tubercle bacilli could not be found in the epithelioid and healing tubercles, but were demonstrated in small numbers in the caseating tubercles. There is, therefore, no doubt as to the nature of the process. The healing tubercles are easily distinguished from small infarcts by their sharply circumscribed borders and by the fibroblastic proliferation of the villi included in the primary intervillous thrombus to form a compact epithelioid mass.

When transition stages from the earliest form of the placental tubercle up to the healing stage are present, as in this material, there is little likelihood that any one who is familiar with the histologic characteristics of placental tubercles would hesitate in immediate recognition of the nature of the process; but if the healing forms alone were present and in small numbers there might be difficulty in such recognition. There are, however, but two things that need to be considered in the differential diagnosis: small localized areas of syphilitic chorionitis and small infarcts showing reparative changes. In the former the syphilitic process involves only the stroma of the villi, and the villi are not fused into a solid fibroblastic or fibroid mass; in the healing infarct the villi may be fused, but there is no fibroblastic formation, or only the slightest, between them.

The healing tubercle, on the other hand, may show outlines of some villi fused into an intervillous epithelioid or fibroblastic proliferation. In this case all stages of tubercles were present, although the majority were in the healing stage, and the presence of tubercle bacilli makes the diagnosis absolutely certain, although the histologic changes are in themselves sufficiently characteristic.

This case, therefore, presents a placental miliary tuberculosis of a low virulence, the majority of the tubercles being in a healing stage. It is very probable, then, that in the earlier months of pregnancy, most likely in the third or fourth month, a latent tubercle in the right apex became active, gave access to the blood of tubercle bacilli that lodged chiefly in the placenta, and produced there lesions that showed a tendency to heal. What other lesions were produced in the body of the mother we do not know. When she left the hospital she showed no signs of any other localizations, and unfortunately no additional history of her or her offspring has been obtainable. This report shows that even in the case of an unrecognized latent lesion in the lung of a pregnant woman tubercle bacilli may enter the circulation and produce a miliary placental tuberculosis. If this is possible it is also possible that under such circumstances the bacilli may pass the placenta and enter the body of the fetus. This case also emphasizes a point that I have made in previous papers on placental tuberculosis, that there is apparently some especial resistance on the part of fetal tissues to the tubercle bacillus, since tubercle bacilli have been found in large numbers in the liver and blood of infants without any histologic appearances of tuberculosis. The low virulence of the placental infection in this case may possibly be explained as the result of such a relative immunity on the part of the placental tissues. On the other hand, as the mother did not develop a miliary tuberculosis, the bacilli may have been of a feebly virulent strain (bovine?), or the number in the maternal blood-stream was small, and those found lodgment only in the placenta.

Reprinted from The Journal of the American Medical Association
Nov. 29, 1913, Vol. LXI, pp. 1951 and 1952

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hyperplastic nodes or blood of the animal from which the inoculation was made.

As far as I have been able to discover, these are the only reports occurring in the literature of changes occurring in the hæmolymph nodes as a result of protozoal infections. My own observations have been limited to the study of chronic malaria in man, and latent Texas fever in the steer (two-year-old immunes).

1. *Chronic malaria.* The malarial material was obtained from Panama, a small number of cases (five) being examined. In these the hæmolymph nodes (formol preparations) were dark grey, somewhat larger than the white lymphatic glands, but not distinctly hyperplastic. (All material had been kept some time in formol.) The microscopical appearances showed in all cases a proliferation of endothelial cells into the blood-sinuses, these being partly blocked by the large pale epithelioid cells, between which lay red-blood cells and pigment-containing phagocytes in great numbers. The lymphoid portions of the nodes were atrophic; no germ centres were seen; and the nodes showed a general lymphoid exhaustion. The one striking change in these glands is the endothelial proliferation into the sinuses, with the presence of many phagocytes containing red-blood cells and hæmosiderin. Eosinophiles are often present in large numbers, and giant cells also occur frequently in the sinuses. The general appearance of these hæmolymph nodes resembles that described by Mallory as occurring in the mesenteric lymph nodes in typhoid fever, and I have no doubt that some, at least, of the nodes seen by him were in reality hæmolymph nodes. In a previous paper I have treated of hyperplasia of the hæmolymph nodes (*Trans. Assoc. of Amer. Physicians*, 1909), and have described briefly this form of endothelial hyperplasia of the sinuses of the hæmolymph nodes as occurring to the most marked degree in certain cases of splenic anæmia and Banti's disease, rachitis, syphilis, chronic tuberculosis, and in the majority of long-continued infections and cachexias.

Such an endothelial proliferation of the blood-sinuses of the hæmolymph nodes is practically always associated with an increased destruction of red-blood cells. The endothelial cells are essentially phagocytic, particularly so for red-blood cells, and their proliferation may be secondary to an increased hæmolysis in the blood-stream. They may, therefore, be simply scavengers and removers of dead blood cells from the circulation, and the occurrence of such a hyperplasia in malaria may be secondary to the blood destruction occurring in that infection. This view is supported by the fact that in all forms of increased blood-destruction these glands show this form of endothelial hyperplasia. But it also occurs in infections and intoxications in which there is no increased hæmolysis, so that it is not improbable that these phagocytic endothelial cells perform a double function of protection and elaboration of blood pigment.

2. *Texas fever.* The material for the study of the reaction of the hæmolymph nodes of the steer to chronic Texas fever infection has been

obtained from certain packing-houses in western cities. It consisted of the hæmolymph nodes, prevertebral fat, and portions of the other organs. The animals were two-year-old Texas steers, Texas fever immunes, practically all coming from the Pecos Valley region. In these animals the cervical, subcutaneous, and prevertebral hæmolymph nodes show a most striking hyperplasia. The nodes are enlarged ten to several hundred times the normal size, the majority as large as cherries, many reaching the size of walnuts, and some as large as an orange. In the white fat of the prevertebral region they make a most striking appearance, as reddish-brown or reddish-blue spheres partly embedded in the fat. They look like small spleens. They are usually round with a very slight hilum on one side, but some are distinctly bean- or kidney-shaped with a well-marked hilum into which vessels pass. The capsule is very thin and tightly stretched. On cross-section the hyperplastic nodes consist chiefly of greatly enlarged blood-sinuses crossed by greyish trabeculæ of lymphoid tissue. The amount of lymphoid tissue is relatively very small compared to the size of the blood-sinuses.

The great hyperplasia of the nodes makes easy the study of their anatomical relationships. The ordinary lymph nodes of these animals are hyperplastic also, but in no degree to be compared to the hyperplasia of the hæmolymph nodes. They are browner in colour than normal lymphatic glands of the steer. In or near the hilum of the lymphatic glands there is always to be found an accompanying hæmolymph node, of much smaller size, usually about the size of a mustard seed or small pea. It is connected with the hilum of the lymph gland by vessels from its capsule. Often this accompanying hæmolymph node is embedded within the substance of the lymph node, but sharply outlined from it by its thin capsule. The hyperplasia of these hæmolymph nodes associated with lymphatic glands is never so marked as that of the solitary hæmolymph nodes in the cervical and prevertebral fat tissues.

The spleens of the steers showing this extraordinary hyperplasia of the hæmolymph nodes were always fibroid, firm, and very brown, and showing marked perisplenitis, hyaline thickenings of the capsule, and adhesions. The other organs show no changes save those of chronic passive congestion and atrophy.

In a personal communication from Meyer, the gross appearance of the hæmolymph nodes in these Texas fever immunes was said to be precisely like the hyperplasia of the same nodes seen in African coast-fever. Aside from this, I know of no other condition in which the hæmolymph nodes of cattle take on such an extraordinary hypertrophy. In the Northern United States it is rare to find in slaughtered animals any marked enlargement of these nodes, and then the enlargement is usually focal and not a generalized one. In such cases there is, however, an associated fibrosis and perisplenitis of the spleen.

The microscopic appearance of the enlarged nodes is very striking. There is a marked hyperplasia of the lymphoid substance, with an increase in the size and number of the germ centres, with numerous mitotic figures, showing increased activity in the formation of lymphocytes. Both central, communicating and peripheral blood-sinuses are enormously enlarged, forming great sinuses traversed by lines of reticulum covered with hyperplastic endothelium. As a rule, few phagocytes are seen in the meshes of the sinuses, and but little blood-pigment is found in the hæmolymph nodes. The ordinary lymphatic glands, on the contrary, contain much hæmosiderin and great numbers of eosinophile cells, in these respects resembling precisely the lymph nodes of the sheep and goat after splenectomy. The hyperplastic germ centres often present as rounded masses directly into the blood of the sinuses, apparently giving off lymphocytes directly into the circulation. The number of lymphocytes in the sinuses is much greater than that seen in the blood-vessels of the lymphatic glands and other organs. The appearances are so striking in this respect that there can be no doubt that the hæmolymph nodes are furnishing lymphocytes in large numbers to the circulation.

No parasites could be demonstrated in the sections of these hyperplastic glands, although the more important staining methods for their demonstration were applied. Unfortunately none of the material was seen by me in a fresh state, and the smears made for me in the packing-houses were not very satisfactory. No parasites were found in them, however. Nothing resembling an involution or resting bodies was seen. No inoculation experiments with these glands could be carried out under the circumstances. According to Meyer, inoculations should convey the disease to susceptible animals in the same manner as in the case of African coast-fever. No parasites or parasite-like forms were found in the spleen or bone-marrow, or in the smears from their tissues. The microscopic sections of the spleen showed a fibrous hyperplasia, lymphoid atrophy, increased pigmentation, and chronic passive congestion. Sections of other organs either showed no changes at all, or a simple atrophy with chronic passive congestion.

The most striking lesion in latent chronic Texas fever infections (so-called immunes) is an extraordinary hyperplasia of the hæmolymph nodes, a condition that, so far as present observations go, has been seen only in piroplasmosis.

The exact position of the hæmolymph nodes in the hæmatopoietic system is still an unsettled problem. Hyperplasia is the chief pathological condition affecting these glands. In man its occurrence in connexion with marked phagocytosis of red cells, and occasional evidences of active myeloid transformation, give these glands a position somewhat between the bone-marrow and the spleen. That they may take on a compensatory function for either seems to be settled by experiment and observation. It is probable that a part of the reaction of the hæmolymph nodes to chronic protozoal infections, as in the case of trypanosomiasis, piroplasmosis, and Texas fever, may be compensatory for the changes in the spleen, and the destruction of red-blood cells found in these conditions. In cattle the hyperplasia of the entire hæmolymph node system is so extraordinary, and so much beyond that seen in other affections of cattle in which the spleen is fibroid and there is excessive hæmolysis, that we must look for some other explanation. This may be found in the fact, as shown by Meyer, that the hæmolymph nodes in African coast-fever contain the parasite in great numbers, and that inoculations of these hyperplastic hæmolymph nodes will transmit the disease from the affected animal to a susceptible one, even when no parasites can be demonstrated in the blood or lymph nodes of the former. It seems safe to infer, then, that this hyperplasia is in part, at least, of the nature of a protective reaction against protozoal parasites in the nodes, and that in trypanosome infections and in African coast-fevers and Texas fever there is an especial tendency on the part of the parasite, in its resting stage probably, to be localized in these nodes. Further investigation of the tropical protozoal infections of cattle should go far towards settling the nature of the hæmolymph nodes, as their number and size in animals makes their study an easy matter.

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Family Susceptibility to Cancer

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Reprinted from
The Journal of the Michigan State Medical
January, 1914
F. C. WARNSHUIS—Editor,
91 Monroe Ave., Grand Rapids, Mich.

FAMILY SUSCEPTIBILITY TO CANCER

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It has long been recognized that a family susceptibility to certain forms of benign neoplasms exists. Many of the peculiar "family marks" or "birthmarks" distinguishing the members of certain family lines are neoplasms usually of a mature connective-tissue variety, chiefly hemangiomas, lymphangiomas or fibromas (moles, warts, nevi, "strawberry mark," "raspberry mark." etc.). Lipomas, chondromas, osteomas, neurofibromas, gliomas, leimyofibromas, papillomas, adeomas, and cyst-adenomas have been observed to "run" in certain families, and most authorities agree as to the existence of a family susceptibility in the case of these neoplasms. Certain varieties of carcinoma and sarcoma are also regarded by various writers as showing a less marked family tendency.

As to a general susceptibility to cancer appearing as a definite family characteristic, authorities at the present time are divided. Its existence is denied by some, and as strongly affirmed by others, but as a matter of fact there are very few good statistical studies of the family occurrence of carcinoma. Cancer surveys have yielded little of value because of the great difficulty in obtaining immediate knowledge of members of a given family for more than one or two generations. It is a well known fact that few hospital patients can give any definite information as to the cause of death of their grand parents, and the same thing is true of the population at large. It is only in rare instances that a complete family history extending over several generations can be obtained. Further, when such rare complete family histories covering a number of generations can be obtained, it must be borne in mind that the diagnosis of cancer a generation or two ago was almost wholly a clinical one, unsupported by microscopic examination; and that the common clinical diagnosis or "tumor" covers a very large and heterogeneous class of conditions, the majority bearing no relationship to carcinoma. It is obvious that such a diagnosis has no statistical value; but, as a matter of fact, many of our so-called "cancer statistics" are based upon just such loose clinical statements. This is, however, no argument for rejecting all of the diagnosis of cancer that have been made without the corroboration of the miscroscopic examination. Particularly in the case of lip, stomach, breast and uterine cancers may clinical diagnoses or family traditions be relied upon with a high degree of certainty. The outward appearances of breast and lip cancers, the striking symptoms of gastric and uterine cancers, in connection with a malignant course and fatal termination offer very fairly reliable criteria for both a clinical diagnosis and family tradition of cancer of these organs; and the percentage of error is probably not very great in so far as these conditions are concerned. In the case of other diagnosis of "abdominal cancer" or "tumor," "cancer of the liver," etc., the precise nature of the affection is very doubtful.

Throughout the literature, particularly that relating to cancer of the breast, there are recorded instances of the multiple family occurrences of cancer. Few of these consider more than the members of the same or of two generations, and usually the affected members alone are taken into account. Such statistics give little information beyond the fact of the multiple occurrence of cancer in certain family groups or generations. Of recorded observations of the multiple occurrence of cancer in one family for several generations the one of Broca (Traité des Tumeurs, 1866, p. 151) is the most important. In brief, this family showed cancer in sixteen out of thirty-seven members, as follows: Madame Z, died at the age of sixty of cancer of the breast. She left four daughters (A, B, C. D) who died of cancer of the liver (2) and cancer of the breast (2) at the ages of 62, 43, 51 and 54 respectively. Madame A had three unmarried daughters, alive and well at ages of 68, 72 and 78 years. Madame B had five daughters and two sons. First son died, without issue, at 54, of cancer of the stomach. First daughter died at 35 of cancer of breast; second at 35-45 of cancer of breast; third, at same age, of cancer of breast: fourth, at same age, of cancer of liver; while the fifth died at 60, non-cancerous. All of the children of Madame B were without issue. Madame C had five daughters and two sons. The first son died in the army without issue; the second son was alive and well at the age of 72. He had one son dying at 18, and one daughter alive and well at 24. The first daughter of Madame C died at 37 of cancer of the breast, leaving two sons and three daughters. The first of these was alive and well at 58, having three healthy sons; a second son died young without issue; first daughter died in child-bed at 28; second daughter died at 49 of cancer of the breast, bearing two healthy daughters; the third daughter died of consumption at 41. Madame C's second daughter died at 40 of cancer of the breast, leaving one healthy son; her third daughter died unmarried, at 47, of cancer of the uterus; the fourth daughter died, at 55, of cancer of the breast, leaving two sons alive and healthy; while her fifth daughter died unmarried at 61, of cancer of the liver. Madame D had an only son alive and well at the age of 70.

Williams (Natural History of Cancer, 1908) has collected from the literature many examples of the multiple occurrence of cancer in families and family groups, and also added valuable observations of his own. In 370 female cancer patients he found a history of heridity in 83 or 22.4 per cent.; in 136 cases in mammary cancer there was a family history in 24.2 per cent., and in 142 cases of uterine cancer a history of heredity in 19.7 per cent. Such percentages, as Williams points out, are very high from whatever point of view they may be regarded. Butlin finds a family history of cancer in 37 per cent. of cases of mammary cancer. Nunn estimates such a family history in breast cancer as 29.3 per cent., and Lemp at 23 per cent., all of these estimates agreeing fairly closely. In certain families, as in Broca's case, the cancer chances are greatly increased, fifteen to twenty times that of individuals of the general population. If the chances of cancer for the individuals of certain families are fifteen to twenty times greater than for the individual of the general population, we must concede the existence of a family tendency to cancer, since such high percentages of occurrence in certain family lines cannot be explained on the grounds of environment, infection, or more coincidence. Particularly is an assumption of a family tendency justified when the cancer affects the same organ or tissue of one sex through a number of generations, as in the case of Warren, the patient, patient's father, grandfather and great-grandfather all dying of cancer of the penis; and another instance reported by Earle of a patient with epithelioma of the scrotum, whose brother, father and grandfather all died of the same condition.

Williams from his own experience and collected cases, therefore, regards the statistical evidence in favor of family susceptibility to cancer as very strong. He states that inherited cancer manifests itself much more frequently in the female, although as often derived from the paternal as from the maternal side of the house. In cases of multiple family cancer there is an especial tendency for the females to be affected. He notes also the atavistic and collateral inheritance of the susceptibility to cancer, and the frequent association of tuberculosis, arthritic manifestations, and excessive fecundity. He believes that the majority of cancer patients are the *surviving members of tuberculous families;* hence advances the proposition that no inheritable condition is more favorable to the development of cancer than that which gives proclivity to cancer. Nevertheless he abstains from interpreting his collected facts in Mendelian terms, although he believes that the time will soon come when it will be advantageous to study the whole question from a Mendelian standpoint. He regards the great prophylactic question to be: "How in breeding to render a dominant tendency to cancer recessive."

Levin (*Zeitschrift für Krebsforschung,* 1912) is the first to make a eugenical study of the influence of heredity on cancer from the Mendelian standpoint. Wtih the assistance of the Eugenic Record office at Cold Spring Harbor, Long Island, he has collected data from five families, two being fairly complete, the other three as yet fragmentary. These families are studied from the broad standpoint of the entire family line for six generations, and then by family groups in which one or more members suffer from cancer. The analysis of the family line as a whole shows that the incidence of cancer is not greater numerically than that of the general population. One thing is brought out in this study that does, however, speak for an influence of heredity upon cancer, and that is the occurrence in certain generations of cancer groups with a cancerous ancestor on either paternal or maternal side, or on both. The percentage of cancerous members in each cancerous fraternity corresponds closely to the Mendelian percentage of members with recessive unit-characters in a hybrid generation, running in the eight cancerous fraternities analyzed from 10-33 per cent. of cancerous members to non-cancerous (Mendelian ratio 25 per cent.). Levin concludes that resistance to cancer is therefore a dominant unit-character, the absence of which creates a susceptibility to cancer. He also notes that the family susceptibility is specific for certain organs, in one family the uterus, in another the breast are the organs particularly involved. This had already been shown by Williams, who also emphasized the fact that in the males of the affected family the gastro-intestinal tract is usually the seat of the cancer, while in the female members the breast or uterus is affected.

A great increase of interest has recently been awakened in the subject of heredity in cancer by numerous observations upon the occurrence of cancer in certain strains of white mice and rats. It has been noted by a number of workers in this line that a greater proportion of spontaneous cancers occurred in mice purchased from certain dealers. While this fact was at first used as an argument for the infective nature of mouse cancer it was shown later that in the case of a strain of mice showing a high percentage of spontaneous cancers a much greater proportion of successful transplantations of the cancer could be obtained than in the case of strains showing few or no spontaneous tumors. According to Leo Loeb the incidence of successful transplantations in some strains showing a high occurrence of spontaneous cancer is practically 100 per cent. In Well's laboratory, breeding experiments with such susceptible strains of mice are being carried out on a large scale, and the facts so far observed speak for the existence of an inherited cancer susceptibility. Although denied by Bashford the occurrence of such a familial tendency to carcinoma in mice is generally accepted at the present time, because of the following observed facts: *Certain strains of mice do not develop spontaneous carcinoma, and such strains are resistant to transplantation of carcinomas from other mice; on the other hand, other family strains of mice show a high frequency of spontaneous carcinoma, and such* *strains give a high percentage of "takes" to transplantations.* Tyzzer has carried out breeding experiments with such strains but was unable to find that such a cancer susceptibility was transmitted according to Mendelian principles. Levin and Sittenfield (Proceedings of the New York Pathological Society, Oct., 1910) concluded from their investigations of the influence of heredity in cancer of the white rat that *resistance to the growth of an inoculable cancer in this animal behaves in the manner of a Mendelian dominat unit-character.* The observations of the part played by heredity in mouse and rat cancer are still too limited for us to draw any final conclusions; but, with the breeding experiments now being carried on, on a large scale by a number of workers, the problem may soon be settled.

In the *"Archives of Internal Medicine," November, 1913,* I have published the results of a statistical investigation of the cases of carcinoma examined in my laboratory during the years 1895-1913 for the purpose of determining what influence heredity might have had in the etiology of these cases. During these years there were 3,600 cases of neoplasm examined in the Pathological Laboratory of the University for the purpose of diagnosis. Of these 3,600 neoplasms 1,600 were carcinomas; and it is with these 1,600 cases that the present investigation was concerned. The great majority, about 90 per cent., of the material came from the state of Michigan; and as the University Hospital is not a charity hospital, it represents very well the average population of the state. The usual difficulty of obtaining a complete family history of hospital patients exists here also, although a teaching hospital and with much greater care taken in this direction than would be carried out in the average city hospital. About 30 per cent. gave full histories with details of several generations; and it is in these detailed histories that evidence of a family tendency to cancer stands out. I have for several years been getting the impression that a family susceptibility to cancer was very striking in some families, and that in such families there was a tendency for the neoplasm to appear at an earlier age in the youngest generation, and to run a more malignant course. Whenever, then, we have had a case of carcinoma in a relatively young individual I have made an especial effort to obtain the family history. As a result our records show an increase in recent years of histories showing a multiple occurrence of cancer.

From the records of the carcinoma cases I have selected the most striking of the cases of multiple family occurrence of cancer. Four families stand out prominently because of the striking proclivity of cancer shown in three generations. Charts illustrating these families are given in the *"Archives of Internal Medicine,"* but the abstract of the family histories is reproduced here.

Family G.—In this family a fairly complete survey was made of the two generations derived from a cancerous grandfather with a traditionary history of career in his life and a grandmother with a normal family history. From these there were ten children, five males and five females. Two of the daughters died of cancer of the uterus at 55 and 40 years, while two sons died at 42 of cancer of the stomach, and a third one at 45 of cancer of the abdomen. All fiive of these individuals were married to normal partners without a family history of cancer, and all had issue, as follows: Oldest daughter who died at 55 of cancer of the uterus, had ten children; one daughter operated on at 42 for "cancer" of the uterus and still living; another daughter operated on at 22 for uterine tumor and bilateral dermoids of ovary, and still living. The remaining eight children are all living and well, only two being over 40 years of age. The second daughter, who died at 40 of cancer of the uterus, had four children, two sons and two daughters, all dying of cancer, the two sons of cancer of the stomach and intestine, and the two daughters of carcinoma of the uterus. The third daughter, living and well at the age of 75, has three normal children living at the ages of 47, 50 and 55. Four children had no living issue. The eighth child, a son, died at 42 of cancer of the stomach. His wife was of normal family history. They had eight children, of whom two daughters have died of cancer of the uterus at 40 and 44 years, while the remaining six are all living and well below the age of 40. The ninth child, a son, died of cancer of the stomach when between 40 and 42 years of age. He left six children from a marriage contracted with a woman of non-cancerous family history. One daughter died at 42 of cancer of the uterus, three children died of tuberculosis between the ages of 18 and 25 years, while two others are living and well at the ages of 32 and 29 years. The tenth son died at 45 of cancer of the abdomen, most probably primary in the stomach. He left, from a marriage contracted with a woman of non-cancerous family, seven children, of whom one died at 42 of cancer of the stomach and liver, another at 47 of cancer of the intestine, while a third was operated on at 42 for tumor ("cancer") of the uterus and still lives in apparent good health. Four others are living and normal at the ages of 45, 35, 30 and thirty.

Of the forty-eight descendants of the cancerous grandfather seventeen have died or been operated on for "cancer." The preponderance of carcinoma of the uterus (ten cases and of the stomach (seven cases) is very striking in the family history.

Family F.—In this family the paternal grandmother died of "tumor." Her non-cancerous brother had two children, both of whom died of "cancer." Her only son died at 61 of dropsy. He married a woman who had two brothers who died of cancer of the stomach. She herself died of Bright's disease at 75. Her mother died at heart disease. The three daughters of this pair who show a double family history of susceptibility to cancer all had neoplasms; the oldest was operated on for tumor ("cancer") of the uterus and is still living; the second was operated on at 51 for myosacroma of uterus, while the third daughter died of cystic tumor of the ovary. In this family history the preponderance of stomach and uterine neoplasms is also shown.

Family P.—The paternal grandfather had a nephew who died of cancer of the lip. In the first filial generation there was one daughter who died at 35 of cancer of the lip and a son who died at 86 of cancer of the scalp and cervical lymph-nodes. This son married a non-cancerous woman whose only sister had died at 47 of cancer of the rectum. From this union thirteen children, ten of whom (five brothers and five sisters) all died of pulmonary tuberculosis before the age of 30, while three remaining daughters had carcinoma of the breast, two dying at the ages of 36 and 42, and one operated on at thirty-five.

Family S.—The paternal great-grandfather died at about 70 of cancer of the stomach. His only son died at about 60 of cancer of the stomach, having married a woman who died at about 50 of cancer of the breast. They had six children, all of whom died of cancer; two daughters died at 80 and 60 of cancer of the breast, and another at 60 of multiple carcinoma of the breast, bladder and rectum. Two sons died of cancer of the stomach at the ages of 75 and 40, the third son dying of cancer of some internal organ, most probably the stomach. Only one son had issue, by marriage with a normal line. The only child died at 36 of cancer of the uterus. Of the eight descendants of the cancerous great-grandfather all died of cancer. As in Family P., the occurrence of carcinoma in both paternal and matermal lines apparently strengthens the susceptibility, both families becoming extinct.

A larger number of cases showing a family history of multiple occurrence of cancer through two or three generations are to be found in our records. Twenty-nine of these were selected as representative. Since the family histories are more or less incompletely given I have classed these histories under the head of "cancerous fraternities" or "cancer-generations." In general the normal members of the second and third generations are given, so that the proportion of cancerous to non-cancerous in two generations at least is exact. It was notable that the great majority of the cancerous fraternities occurred in small families; and in many of these the patient from whom the maaterial examined for diagnosis came was the surviving member of the family line. In families showing these cancer-generations the carcinoma may appear in three or four generations, or there may be an intervening generation the members of which are not cancerous or more rarely a collateral transmission may be shown. In some cases all of the members of the small family are cancerous. By far the great majority of these are females; and the family is in a large proportion of cases brought to an end by death of its female members through carcinoma of the breast or of the uterus.

The results of our study of this material may be summed up as follows: In the histories of the cancer cases coming from the state of Michigan and examined at the Pathological Laboratory of the University about 15 per cent. show a striking history of multiple family occurrence. When the difficulty of obtaining good histories is considered this proportion is relatively high; and, on the whole, corresponds fairly closely with the percentages obtained by Williams. We must conclude, then, that a definite and marked susceptibility to carcinoma exists in certain families and family generations. This family tendency is usually most pronounced when there is a history of cancer in both paternal and maternal lines. In such families there is an especial tendency for carcinoma to appear at an earlier age than in the forebears, and in these younger individuals the cancer usually shows an increased malignancy, developing more rapidly and setting up general metastases more quickly than in cases from which we can obtain no family history. Whenever we have a case of carcinoma appearing in an individual before the age of 35 we take especial pains to look up the family history with this especial point in mind to determine if there has been a history of cancer in previous generations; and in a relatively large number of cases this has proved to be the case. I therefore consider the prognosis bad in those cases of carcinoma in relatively young people who have a family history of multiple occurrence of cancer. This is also true in the cases of carcinoma coming from families where there is a history of tuberculosis on both sides. Our results corroborate those of Williams. We find that tuberculosis is the most commonly associated family disease in families having a multiple occurrence of carcinoma and that in many cases cancer terminates a family line that has suffered severely from tuberculosis. The association of the two diseases in families showing our cancerous fraternities is very striking. We also find, as did Williams, that many of these families a few generations back showed a high grade of fertility with large families of children, but that in the present generation there is a markedly lessened fertility and in many cases the cancerous individual terminates the family line. Family susceptibility to carcinoma we find to be shown in carcinoma of the breast and uterus in females and of the mouth, lip, stomach and intestines in the males. Rodent ulcer affecting some portion of the face shows frequently a history of multiple family occurrence in several generations. In the more complete family records studied the carcinoma manifests itself in the breast or uterus in the female usually, and in the gastro-intestinal tract in the male. This specificity of location has been noted by Williams, Levin and others. Next to tuberculosis we have found cardiac and renal disease most frequently associated with a family history of carcinoma.

Giving due consideration to possible errors in diagnosis in previous generations and the difficulty of obtaining accurate histories, I am still convinced that there is a definite and well marked family susceptibility to cancer in many family lines; and I think it is very probable that if we can have better and more complete histories the multiple occurrence of cancer in family lines would be found to be very much more frequent than our histories now show. I think we are perfectly safe in concluding that certain families show a definite cancer susceptibility and that this is inherited often in a progressive rate of inheritance, the susceptibility being dominant rather than recessive, as Levin concludes from his study. I do not think that the data are at present sufficient for us to apply the Mendelian principles to cancer heredity. Some of my cases agree fairly well with Levin's, the percentage of cancerous members in each cancerous fraternity corresponding fairly closely to the Mendelian percentage of members with recessive unit characters in a hybrid generation. If I considered the data sufficiently conclusive for any generalization, I would say that they point toward the existence of a progressive generative inheritance, the running out or extinction of a family line through the gradual development of inferior stock from an inheritance of susceptibility to tuberculosis and cancer, such an extinction often developing in two generations in a family previously marked for excessive fertility and longevity.

With the growing interest in eugenics and in family records very careful attention should be paid to all of these points, and in hospitals such as the University of Michigan Hospital, where such a large amount of cancer material is seen, a special effort should be made to collect accurate data concerning the families of cancerous patients. When such data are obtainable definite conclusions may be drawn.

DISCUSSIONS.

DR. CHARLES B. G. DENANCREDE: This paper is of great interest. The method employed by Dr. Warthin is to be commended, provided we bear in mind the fact that we never can correctly estimate the natural history of carcinoma or the unquestionable results of treatment until we understand the cause of cancer. Again, we cannot be certain of our pathologic data until two or more generations of competent pathologists have examined every specimen adequately, included in the statistics, because too many museum specimens now exist, which can yet be correctly diagnosed, which would be found incorrectly labelled if studied by a modern pathologist.

Dr. Warthin, when studying the eighteen hundred cases which have passed beneath his scrutiny during the past eighteen years, excludes two-thirds because the histories are inadequate, taking about six hundred, where the data seems fairly reliable. Of these, however, only about fifteen per cent. apparently demonstrate his views as to heredity. Of the cases with acceptable histories the majority were treated by me and in my service at the University Hospital. I regret to state that I am confident that many of the histories of my cases in the accepted class were decidedly unreliable and that of the remaining eighteen hundred thoroughly reliable accounts, if securable, might either enormously reinforce Dr. Warthin's arguments, or equally likely weaken his contentions. I have so often found my students' histories so misleading for even a clinical diagnosis, that when reliable evidence as to family history is requisite, ,I have to sift all the evidence myself, often being able to arrive at no conclusion or perhaps one absolutely different from that arrived at by the historian. I have a very distinct opinion regarding the lack of proof as to the hereditary nature of carcinoma, despite my early teaching that this was an unquestionable fact. Many of our convictions cannot be proved by actual evidence in our present state of inadequate information. If the experience of forty-odd years have radically changed my opinion on this point there must be reliable grounds for such a change of front, which should have some weight.

I am also inclined to give some weight to the possible failure to eliminate from our historical, and their therapeutic statistics, the fatalities resulting from operations and their complications; were these always deaths from carcinoma, or were they assumed to be because of the fatal results, without adequate histologic examinations? Again, if these patients had not died as the result of operation, might not some of them really proved to have been cures, so vitiating the mortality results? These, and other objections must in all honesty be carefully weighed when attempting to decide any question merely or chiefly by statistics. The rather curious association of tuberculosis and carcinoma, which in my professional youth was denied as a possibility, has been verified in a number of patients, the specimens of which have been reported upon by Dr. Warthin.

I have been greatly impressed by the data presented by Dr. Warthin and hold myself ready to review anew my conclusions concerning the whole subject of carcinoma.

I trust that I shall not be understood as arriving at my conclusions concerning carcinomatous heredity from the six hundred cases included in Dr. Warthin's expurgated statistics, or the probable one thousand cases where I have been the operator or have in some way been cognizant of the patients, but what I learned in my hospital and private experience of the more than twenty years before I came to Ann Arbor.

Dr. Cyrenus G. Darling: While listening to Dr. Warthin's very able address, two points came to my mind. He says that the German cancer survey was without benefit, but he has not stated that a properly conducted survey might not be useful. Why not have such a Michigan cancer survey? Why should not such an important project originate in this Society? We know little or nothing about the results of our numerous operations for this disease, except in a few cases in our own immediate neighborhood. A survey might enable us to determine some of the important facts. It would be well for Dr. Warthin to prepare a list of questions which should be answered by every cancer patient coming to the University Hospital. This paper should be left with the house physician and made out by him as a part of the admission history.

Dr. Udo J. Wile: I have been amazed at the relatively large number of cases of cancer of the skin that occur in this vicinity. In a clinic in New York in which over three thousand cases were treated each year I can recall but three or four cases of epithelioma. During the past year at the University Hospital of over eight hundred cases treated there were forty-four cases of cancer of the skin. We have been careful to note in these cases the occurrence of any family history. Offhand I should say that about 15 per cent. give ahistory of cancers in other members of the family. Curiously enough these have been for the most part cancers of the skin also, rather than visceral neoplasms. We have also noted that the occurrence of cancer in the patient's family has usually been on the maternal side. I should be glad to turn over these records to Dr. Warthin should he desire them.

9

The Minute Changes Produced in Leukemic Tissues by Exposure to Röntgen Rays

BY

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FROM THE
AMERICAN JOURNAL OF THE MEDICAL SCIENCES
January, 1914, No. 1, vol. cxlvii, p. 72

Extracted from the American Journal of the Medical Sciences,
January, 1914, No. 1, vol. cxlvii, p. 72.

THE MINUTE CHANGES PRODUCED IN LEUKEMIC TISSUES BY EXPOSURE TO RÖNTGEN RAYS.[1]

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The changes produced by Röntgen irradiation in the blood-forming organs of experimental animals have been fully described by Heineke, myself, and other observers. In previous reports[2] the writer has also described the changes produced in the tissues of leukemic patients by prolonged exposure to these rays. Since that time he has had additional opportunities of examining the tissues of leukemic cases treated in this manner, in all the autopsy material of eight cases of myelemia, two of lymphemia, three of Hodgkin's disease, and a number of lymph nodes and spleens taken from such cases. These cases present, therefore, a varied range insofar as the period of irradiation is concerned; in some, the tissues show the early action of the rays; in others, the changes are those produced by irradiation extended over periods of one year, eighteen months, and two years. As a result of this study, it has been possible to separate the immediate and remote effects of the irradiation, and to distinguish the changes so produced into two classes: *immediate* or *degenerative* and *reactive*. A number of interesting observations have been made during the investigation, and it seems worth while to present here in condensed form the total results of these observations.

The immediate action of Röntgen rays upon the tissues of leukemia is a degenerative one. Cells are either killed outright or are so damaged that they die within a short period, both cell body and nucleus showing rather specific changes, so that it is possible to distinguish these degenerative changes from those produced in leukemic tissues by infections or other injurious agents. The cells so injured are the small and large lymphocytes, myelocytes, myeloblasts, large lymphocytes, and to some extent, also, the polynuclears. After a prolonged period of irradiation there comes an apparent period of adjustment to this destruction, the tissues contain fewer evidences of cell death and degeneration, but also fewer proliferating cells. In the blood-stream the number of white cells may decrease to normal or below normal; but it may, on the other hand, steadily rise until the number is much greater than before the irradiation, that is, a leukemic condition of the blood may be reduced to an aleukemic under the progress of the treatment or the reverse may take place. In the cases dying after prolonged treatment with Röntgen rays the character of the cells in the spleen, lymph nodes, and bone-marrow is different from that of these organs in patients who have received no Röntgen-ray treatment. Upon these differences we base our description as follows:

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[1] Presented before the Section of General Pathology, XVII International Congress of Medicine, London, August, 1913.

[2] International Clinics, 1906; Trans. Amer. Röntgen Ray Soc., 1906.

I. Degenerative Changes. As the result of single exposures, or of several within a relatively short period of time, the tissues of the lymph nodes, spleen, and bone-marrow, in the order given, show patches of degenerating cells, as manifested by nuclear fragmentation and swelling of the celll. In the earliest cases the nuclear membrane of the cells (lymphocyte, myelocyte, etc.) is preserved, the nucleus swollen, with fragmentation of its chromatin, into spherical granules of varying size. The protoplasm may show no changes or become clearer, often vacuolated. The cell so damaged does not show these changes immediately after the irradiation, but usually within ten to fourteen days. The injured cells then rapidly split up into fragments, all traces of the protoplasm are lost, and only the chromatin granules remain, often as "chromatin dust." This injury to the cell is not a diffuse one; apparently only certain cells are affected, as many cells apparently normal are found near the degenerating cells. In the lymph nodes the degenerating cells may be found especially in the germ centres if these are still preserved, but after a time they are found all thorough the node. Repeated exposures cause an increase in the number of the degenerating cells, the greater part of the gland may become necrotic, in some glands all cells may be killed, and a caseous detritus finally takes the place of the cells of the node, the connective-tissue capsule gradually becoming thicker. These changes are more marked in the lymph nodes of Hodgkin's disease and lymphemia than in those of myelemia. In the spleen the reverse is apparently true; the myelemic spleen shows greater cell-degeneration and cell-necrosis than does the lymphemic spleen. The atypical myeloid cells in this condition suffer chiefly, especially the large bone-marrow lymphocytes, or myeloblasts. The myelocytes and cells of the type of bone-marrow giant cells also are easily killed and disappear, until finally all atypical myeloid cells in the spleen may be entirely absent, and the spleen appear as a fibroid organ containing scattered lymphoid cells. The reduction in size of the myelemic spleen may, therefore, be considerable, and in our experience is always greater than that of the lymphemic spleen. Similar degenerative changes occur in the bone-marrow, but are less marked. It is much more apparent in myelemia than in lymphemia.

Lymph nodes removed some months after continued irradiation for short periods daily show in lymphemia and Hodgkin's disease many large cells containing a diffusely staining or granular protoplasm. Areas of cells containing numerous fat droplets begin to appear, and finally the nodes may contain large areas of fatty degeneration. The vacuolated cells may ultimately go to pieces and large fat droplets remain in the tissue detritus. Cholesterin crystals soon form in these, so that it is not uncommon to find in the irradiated glands of lymphemia and Hodgkin's disease areas of caseation containing fat droplets and cholesterin clefts. Even under the continued irradiation, foreign-body giant cells may develop in these areas. In some glands all of the cells finally assume the type of large, pale lymphocytes, with vacuolated protoplasm. The writer has never found these fatty changes in the lymph nodes of myelemic cases.

In the blood-smears made from myelemic and lymphemic patients the reduction in the number of white cells with a great increase in the number of degenerating forms are the chief changes observable. The reduction in lymphemia is not as striking as it is in myelemia; on the contrary, the number of small lymphocytes in the blood may steadily rise in spite of the irradiation; and in one case of Hodgkin's disease irradiated over a long period of time, the blood which showed no leukemic characteristics at the beginning of the irradiation gradually took on the characteristics of a lymphatic leukemia, with great numbers of large lymphocytes in the circulating blood. There is apparently a limit to the degenerative action upon the white cells and blood-forming organs during irradiation; and after a certain time some adjustment or reaction to the irradiation apparently takes place.

II. Reactive Changes. The reactive changes are shown by a diminution in the number of degenerating and necrotic cells in the blood-forming organs, and in a change in the type of cells forming the bulk of these tissues. In lymphemia and Hodgkin's disease the reaction takes place much more quickly than in myelemia. Around the necrotic glands in the first-named condition there is regenerated a new and atypical lymphoid tissue characterized by a great number of atypical large lymphocytes, of a character resembling the maternal lymphocytes of hyperplastic germ centres, seen in chronic inflammations of the tonsils and other lymphoid tissues. These cells have a granular cytoplasm, staining more heavily with eosin and hematoxylin, and with granular nuclei. This newly formed atypical lymphoid tissue may infiltrate the capsule of the lymph node and extend into the necrotic area, replacing it in part; or if it begins within the lymph node it may infiltrate through the capsule into the surrounding tissues. New areas of atypical lymphoid tissue develop in the cervical, axillary, and prevertebral adipose tissue. In these new areas vacuolated cells are very common, as are also large, pale cells of endothelial type. Collections of hyperchromatic cells with large irregular nuclei occur throughout this new tissue. In the lymph- and bloodvessels of this tissue there is a great increase in cells of the atypical lymphocyte character.

In the case of myelemia treated over long periods of time the peripheral lymph nodes may show at death little change except a poverty in germ centres and an absence of cells of the bone-marrow group. The retroperitoneal hemolymph nodes may show a marked hyperplasia of atypical cells resembling the large lymphocytes of the bone-marrow. All distinction between the cords and trabeculæ and sinuses is lost; the entire gland is made up of densely packed cells that infiltrate through the capsule and into the neighboring fat tissue. The bloodvessels may or may not show any increase in the number of white cells, but usually contain cells of the large lymphocyte type. No other cells of the bone-marrow group are found in these hyperplastic prevertebral glands. I have not found in my cases as marked an atypical regeneration of leukoblastic tissue in the spleen as in these glands. In some cases the spleen is fibroid to the end, with few or no cells that can be regarded as myeloid in type. In two cases large areas of caseous necrosis, hemorrhages, and anemic infactions, associated with thrombosis of the splenic vessels, were present. One case showing these changes in a marked degree died from a rupture of a splenic artery, the spleen at autopsy being embedded in a large clot proceeding from a small opening in the capsule of the organ communicating with a small-sized artery. The arteries of the spleen showed an obliterating endarteritis, and the majority of the smaller vessels were thrombosed. No myeloid tissue was present in the organ, although the other organs of the body presented the usual appearances of leukemia.

The changes in the bone-marrow resemble those in the retroperitoneal hemolymph nodes in those cases in which the leukemic condition of the blood had changed to an aleukemic under the treatment. Cells of myeloid type were present in greater numbers, but the chief cell of the marrow was the large pale lymphocyte (myeloblast?). In no case treated by Röntgen irradiation were the conditions in the hematopoietic organs changed to a normal condition. The effect of the treatment is essentially degenerative and inhibitive, but the essential leukemic process goes on unchecked, although greatly modified. The treatment is, therefore, not curative; and such a result we no longer expect from our clinical failures.

In the first stages of the treatment the leukemic tissues show great degeneration and destruction of the white-cell-forming tissues. It may completely disappear from the spleen, and the processes of white-cell formation may be so inhibited that an aleukemic condition of the blood may result. After some months there arises a more undifferentiated leukoblastic tissue, particularly in the retroperitoneal hemolymph nodes and in the bone-marrow; the leukemic condition of the blood may return or it may not. With an increasing cachexia the process may be terminated by symptoms of intoxication, or by some secondary event, as hemorrhage from the necrotic spleen. The changes in the kidney, which may be very marked (cloudy swelling, simple necrosis, and calcification), may also in part be responsible for the fatal termination.

In conclusion, prolonged irradiation of the hematopoietic organs in leukemia causes first a degeneration of the young and maternal cells, leading to a great decrease in the output of leukocytes, particularly in myelemia. To this destructive effect there follows a reaction in which cells of a more resistant type are formed, and the essential leukemic process remains unchecked, although altered in character.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Edited by GEORGE MORRIS PIERSOL, M.D. Monthly. Illustrated. 1920 pages yearly. Price, $5.00 per annum.

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Primary Tissue Lesions in the Heart Produced by Spirochete Pallida

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FROM THE
AMERICAN JOURNAL OF THE MEDICAL SCIENCES
May, 1914, No. 5, vol. cxlvii, p. 667

Extracted from the American Journal of the Medical Sciences,
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PRIMARY TISSUE LESIONS IN THE HEART PRODUCED BY SPIROCHETE PALLIDA.[1]

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All recent statistics show a marked increase in the occurrence of cardiac disease, and various theories have been advanced to explain this increase. Alcoholism, nicotinism, nervous strain, overeating and drinking, intestinal intoxications, chronic infections, etc., have been given as the factors responsible for the myocardial affections that are seen with an apparently increasing frequency, but there is little unanimity of opinion as to the relative importance of these etiological agents. That syphilis plays an important role in the production of cardiac disease has long been suspected, and statements to this effect occur in the majority of text-books, usually unsupported by any pathological evidence. The truth of the matter is, that before the discovery of the Spirochete pallida as the etiological agent of syphilis, the pathologist himself recognized but few lesions of the heart as essentially pathognostic of syphilis. As to the significance of the gumma, he had no doubts; but gummas of the heart are relatively rare, hence his actual proof of cardiac syphilis became restricted to those instances in which the gumma was present. The frequent association of forms of chronic myocarditis, fibroid heart, anemic infarction of the myocardium and coronary sclerosis, with other pathological evidences of syphilis elsewhere in the body, such as tabes, paresis, gumma of the brain or liver, aortic aneurysm, bone lesions, orchitis fibrosa, etc., has given the pathologist a strong leaning to the view that the heart is one of the most frequently affected organs in syphilis. In my own experience this has been the case, and I consider the most frequent pathognostic lesion-complex of syphilis to be that shown by the heart, aorta, and the orchitis fibrosa syphilitica of the testes. To these, a fourth lesion could be added as next in constancy of occurrence, the presence in the adrenals of small areas of plasma-cell infiltration.

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[1] Presented before the Section of General Pathology, International Congress of Medicine, London, August, 1913.

That these lesions are actually syphilitic could only be assumed upon the strength of circumstantial evidence before the demonstration of the Spirochete pallida gave us a positive finding by which the diagnosis of syphilis could be made absolute. The whole pathology of syphilis must then be worked over from the standpoint of this new criterion, and this is particularly true of the affections of the heart long supposed to be syphilitic, but which from their nature could not be positively determined to be so. From this point of view I have been for several years engaged in a study of cardiac syphilis based upon the occurrence of the Spirochete pallida in the tissues of the heart, and the results of this study, insofar as the primary tissue lesions of the heart muscle are concerned, I wish to give here in a condensed form.

The material studied consists of two hundred hearts, fifty of congenital syphilis and one hundred and fifty of acquired syphilis. They represent all ages and all stages of the disease; the congenital cases are mostly newborn and young children, the acquired cases mostly adults in middle life with a history of old infection. The number of active secondary stage cases in the adult is small, but sufficient to trace the development of the lesions through successive stages. The Levaditi method in its original form has been used chiefly in this work, as it still remains the most satisfactory method for the demonstration of the spirochete in sections. For the study of the tissue changes themselves the ordinary staining methods have been employed, with resort to special stains for special purposes, whenever this was considered necessary to determine the nature of the lesion. As a result of this study the primary lesions of cardiac syphilis may be described as follows:

PARENCHYMATOUS. *Localizations of Spirochetes in the Myocardium without Recognizable Tissue Lesions.* Large colonies of spirochetes may be found in the myocardium, either in the tissue spaces of certain muscle areas, or about the bloodvessels, without any changes in the neighboring heart muscle that can be recognized by any of the technical methods employed at the present time. The muscle stains as well as normal heart muscle; it contains no vacuoles or granules, and presents all the appearances of normal muscle. The spirochetes lie in the intermuscular spaces, often in great numbers. Sometimes they appear within the muscle substance, as shown in cross-sections, but this is not common. Such findings are most frequent in congenital syphilis, but such collections of spirochetes without recognizable myocardial changes are found also in acquired syphilis, particularly in active secondary stages or early tertiary.

Pale Degeneration of the Heart Muscle in Association with Spirochete Pallida. One of the earliest recognizable changes in the heart muscle in areas containing spirochetes is the loss of color in the muscle fiber and its failure to take eosin in the normal way. Compared with normal areas, such affected muscle appears light and clear, with a loss of its striations, and shows vacuolated or light-staining nuclei. In the severe grades of this change the muscle passes so insensibly into the connective tissue that it is difficult to separate the two, so closely do they come to resemble each other in ordinary stained sections. Vacuoles may or may not be present in these fibers. The appearance of the fiber is not wholly like that of Zenker's necrosis, as it is less waxy or hyaline, appearing "washed-out." The fibers are also smaller than normal. This form of degeneration may occur as a purely parenchymatous change, but is most commonly associated with interstitial changes, particularly with the mucoid edema so frequently seen in congenital cases. This change is probably to be interpreted as being of the nature of a serous atrophy or liquefaction necrosis, but there is never any fraying-out of the cell protoplasm as in ordinary liquefaction necrosis.

Fatty Degeneration. A marked fatty degeneration of the cardiac muscle is often the only tissue lesion associated with the presence of the spirochete colonies in the myocardium. It occurs as a focal change, visible to the naked eye as yellowish pin-head spots, but often larger. Microscopically, the fibers are atrophic and filled with large droplets of fat, the droplets, as a rule, being larger than those commonly seen in fatty degeneration of the heart muscle in such conditions as anemia, phosphorus poisoning, etc. Usually two or three large vacuoles replace the cytoplasm. This fatty degeneration of the fibers occurs also in the muscle surrounding the areas of interstitial infiltration and proliferation. In these areas of fatty degeneration, fewer spirochetes are usually found than in the focal areas of fatty degeneration unaccompanied by interstitial changes. In the case of severe vascular and perivascular infiltration and proliferation, irregular areas of fatty degeneration occur along the affected areas, but this is probably a secondary change to the circulatory disturbance. In the focal areas without other changes than the mere presence of the spirochetes, the occurrence of the fatty change must be explained as due to the presence of the organism, the latter probably robbing the tissues of their oxygen and food supply. Following the focal fatty degeneration, there may occur later a deposit of lime salts, so that focal areas of calcification can be produced by syphilis, and their occurrence in the myocardium should lead to a suspicion of this infection.

Simple Atrophy. Colonies of spirochetes can sometimes be located by the presence of focal areas of simple atrophy, the muscle showing no other change than a marked reduction in size. The interstitial substance may or may not be increased or show proliferation, and the pale degeneration and fatty degeneration may be associated with the atrophy.

Necrosis. In virulent cases of congenital syphilis in which the tissues of the body show enormous numbers of spirochetes, yellowish or light-colored areas may be found in the myocardium as well as in other parts of the body. These areas rarely exceed 5 mm. in diameter, and are usually much smaller. In the heart the muscle in these areas appears as fine fibrillæ without nuclei, or is entirely absent, its place being taken by a collection of lymphocytes, plasma cells, and fibroblastic cells. Around the borders fibers showing transition stages of liquefaction necrosis are seen, and the surrounding tissue appears as in a chronic edema, the tissue elements being pushed apart and the spaces filled with a fine albuminous precipitate, a mucoid substance and cells. With the specific mucin dyes, as kresyl violet, reactions for mucin are almost always obtained in these areas of liquefaction necrosis. Such changes are absolutely independent of any vascular changes, and are wholly the result of the spirochetes that lie packed in great numbers in these necrotic areas.

INTERSTITIAL CHANGES. *Edema.* In syphilitic hearts, particularly in congenital syphilis, pale areas, moist and translucent, may be seen even with the naked eye, or the entire heart wall may be very pale, translucent, and moist. On microscopic examination the pale foci are found to be areas in which the changes are wholly suggestive of edema. The muscle fibers are pushed apart, the reticulum is fibrillated and contains fine granules, and the number of wandering cells is more or less increased. The presence of fat vacuoles in the muscle fibers adds to the general picture of a severe local edema, so that the average observer would pass it as an edema. But the Levaditi preparations show these apparently edematous areas to be filled with spirochetes, and the mucin tests show frequently the presence of a mucin-like substance, so that the edema is more of the nature of a myxedema. In these areas the spirochetes often appear closely applied to the capillary walls. Some of these areas are relatively poor in cells, but the majority show a fibroblastic proliferation, large, pale, epithelioid cells occurring, their cell bodies lightly staining, and their whole appearance washed out. Mononuclear white cells, plasma cells, and lymphocytes are present in varying numbers; and every transition exists between these pale, non-cellular, watery areas and those containing many cells.

Interstitial Proliferation. This may occur as the first recognizable tissue lesion, but usually after it has reached a certain point the parenchyma shows degenerative changes also. In the heart the proliferation appears to be always primarily vascular or perivascular, the endothelial cells of the capillaries proliferating and forming rods and groups of pale epithelioid cells, the capillary becoming thicker and thicker as the mass of cells in its walls increases. Now capillaries are produced and the area may come to be highly vascularized, but the new vessels are quickly obliterated by the proliferation of the wall. In the larger vessels, particularly in the arterioles, the proliferation is almost wholly perivascular and the spirochetes are found in great numbers in the perivascular lymphatics. Later these areas may become fibroid, and every possible transition stage is found between the focal edemas, and the areas of proliferation that may be interpreted as non-caseating gummas when sharply localized. In the congenital syphilis cases caseation of these areas must be very rare, as we have never found it. Such areas of proliferation without caseation exist also in acquired syphilis.

Myxoma-like Areas. A striking finding in the hearts of congenital syphilis is the occurrence of round, translucent areas that microscopically suggest myxomas and have been mistaken for such. With ordinary stains, hematoxylin and eosin, they appear as sharply circumscribed, spherical areas in which the heart muscle fibers have practically disappeared, only a few atrophic fibrillæ being left. A gelatinous tissue containing branching epithelioid cells and lymphocytes forms the main part of the area and new capillaries occur in it. Mucin tests show the presence of a large amount of mucin, so that the resemblance to a myxoma is greater still in preparations stained in this manner. Levaditi preparations show the presence of spirochetes in varying numbers in these areas, although the number is usually not so great as in the focal fatty areas and edemas. It is probable that the infection is a less virulent and more sharply localized one. These areas may be regarded as young or undifferentiated gummas, myxogumma, without fibroid change or caseation, the tissue remaining in a fibroblastic semigelatinous state. The infiltration of lymphocytes and plasma cells is often very slight, so that this adds to the deceptive appearance of this formation, and if the Levaditi method for the demonstration of spirochetes were not carried out, the true nature of the process would not be detected.

CONCLUSIONS. These studies of cardiac syphilis would show that the primary lesions produced by the Spirochete pallida may be either parenchymatous or interstitial. The parenchymatous lesions are a peculiar pale degeneration, fatty degeneration, simple atrophy and necrosis; the interstitial lesions are the occurrence of a peculiar form of edema (myxedema), vascular and perivascular infiltration, and localized myxoma-like formations. The parenchymatous changes may occur absolutely independently of the interstitial, and the latter may be found with no associated changes in the neighboring heart muscle. The more marked the interstitial changes the more likely are parenchymatous changes to be associated with them, but the most marked parenchymatous lesions may occur without any interstitial changes. The purely parenchymatous lesions are found especially in virulent congenital and active secondary and early tertiary syphilis; in milder and older infections the interstitial changes, particularly the localized vascular and perivascular proliferations, predominate. The myxoma-like formations resembling undifferentiated gummas also occur in more localized and milder infections.

It is also of great importance to know that the heart is so frequently the seat of spirochete localization. The cardiac localization of spirochetes we have found to be more common than the hepatic. Spirochetes may be found in great numbers in the heart when no others can be found elsewhere in the body. In such cases the cardiac muscle may also show no lesions that, according to the older knowledge, would be classed as syphilitic, indeed, no organ or tissue may show any histological signs of syphilis even when the organisms are present in great numbers. That syphilis can produce purely parenchymatous lesions primarily in the myocardium opens up greatly the possibilities of this infection as a factor in the increasing myocardial affections of unknown origin. To what extent the Spirochete pallida is the etiological agent in these conditions cannot be estimated with certainty at the present time, but my own experience would make me believe that syphilis, both congenital and acquired, is the most important etiological factor in the production of cardiac disease, both myocardial and endocardial.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Edited by George Morris Piersol, M.D. Monthly. Illustrated. 1920 pages yearly. Price, $5.00 per annum.

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